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Number 1

BOSTON

presented at a meeting of the New England Surgical Society New
 h Connecticut October 2 1948
 Assistant professor of surgery Harvard Medical School consultant
 branch section chief in surgery Branch No 1 Veterans Administration

medical schools. The other four are associated with medical schools: Newington, Connecticut, under Yale; White River Junction, Vermont, under Dartmouth; and Cushing and West Roxbury under a joint committee from Boston University, Harvard and Tufts.

A most praiseworthy feature is the comparative autonomy of the medical schools. They have no contract with the United States Government, but they have complete responsibility for all professional appointments in the affiliated hospitals. Consultants and attending surgeons and physicians are nominated by the dean's committee. The appointment of the full-time professional chiefs is authorized by the Veterans Administration only after approval by the dean's committee, the Branch Medical Director and the Hospital Manager. Residents are selected by the chiefs of services with the approval of the dean's committee. Furthermore the medical schools through the dean's committee and the professional staffs are authorized to supervise the teaching programs and to direct the expenditure of research funds. Thus, without asking anything in return the Government has given the professional supervision of the affiliated hospitals to the medical schools.

In addition to the consultants appointed by the medical schools there are, as mentioned above, those appointed by the Veterans Administration to act as professional advisers to the Chief Medical Director in Washington and to each of the 13 regional divisions of the Veterans Administration, the branch offices. The national or central office consultants are chosen by the Medical Director in Washington. The branch consultants are appointed by the Chief Medical Director after recommendation by the national consultants and with the approval of all the medical schools in that particular branch. They make detailed surveys of all hospitals in their respective fields and render reports to the branch director. They have direct professional supervision of the nonaffiliated hospitals. However, lest they interfere with the dean's committees they have no professional authority over the affiliated hospitals. As there is no established channel for direct communication between the branch consultants and the dean's committees occasional misunderstandings have arisen and in some areas it has been suggested that the former restrict their activities to the nonaffiliated hospitals.

Actually, the branch consultants, by visiting all the hospitals and maintaining a close contact with the administration, should acquire a valuable breadth of view and be in a position to clarify many problems that appear to be administrative but affect the care of patients. A recognized channel of communication between the dean's committee and the branch consultants would lead to a better integration of the consultant program. The simple expedient of having the senior consultants ipso

facto members of the respective dean's committee would avoid an unnecessary link in the chain and would provide a ready means of contact between the branch consultant and the dean's committee. In hospitals where the senior consultant in surgery is a member of the dean's committee (Yale, Dartmouth—Fig. 1) such a contact has naturally developed and has been mutually beneficial.

An immediate result of the affiliation of Veterans Administration hospitals with the medical schools was an extraordinary improvement in caliber of the professional personnel. In 1945 there was hardly a qualified surgeon in the New England Branch. There were none recognized as such by the American Board. Now all the full-time chiefs of surgery in the affiliated hospitals are well known men with distinguished records of individual accomplishments. Assisted by able consulting and attending staffs, they have established surgical services comparable to those in the best university hospitals.

The part of the hospital consulting and attending surgeons is a vital one. The consultants are men with established reputations as surgeons and teachers. They supervise the teaching, act in an advisory capacity and occasionally carry out surgical procedures of an unusual or formidable nature. In short, they bring the medical school to the hospital. The attending surgeons, in general, a younger group, free from administrative responsibilities, they do the bulk of the daily bedside operating-room instruction but do very little surgery themselves. It may be well to emphasize that an attending surgeon cannot be a man of limited experience hoping to broaden himself by operating in the Veterans Administration hospitals. He must be an accomplished surgeon, capable and willing to teach. His role is a comparatively selfless one.

The consulting and attending surgeons receive a per-diem allowance of \$50 and \$25, respectively, for their services. Since each visit consumes the better part of a day in ward rounds, at clinics or in the operating room the financial return cannot compare with that in private practice. Moreover, in assaying the cost of the consultant program to the Government one must remember that prior to the new regime a consultant was paid for his services by the operation. He might receive as much as \$500 for a major procedure. Now he conducts rounds, gives a clinic and assists at or performs the surgery for \$50 or \$25.

The accomplishments of the reorganized Department of Medicine and Surgery are best measured by improvements in the standards of care offered to the veterans. A detailed comparison between the old and the new would serve no useful purpose and is hardly possible since the older records are not adequate for analysis. The figures from a survey of the hospitals (Table 1) are indicative of the general trend showing a large increase in the volume

clinical material, a reduction in the number of deaths and a gratifying increase in the percentage of autopsies performed.

The record at present speaks for itself and since the findings appeal to the surgical mind more than a bare list of figures, a broad indication of the type of surgery now being done in the affiliated hospitals is presented in Table 2. The data include all opera-

TABLE 2 Comparative Statistics in a Veterans Administration Hospital

DATE	1945	1947
	582	5699
	201	150
	42 (20%)	110 (73%)

performed for gastric or duodenal ulcer in the two years in this branch. Since patients are usually admitted to these hospitals unless their symptoms indicate failure to respond to therapy, the number of cases in which surgery was done iservative. Time does not permit a detailed breakdown of the material, but the figures for gastric resection include 2 for gastrojejunocolic and 8 for acute massive hemorrhage. The

TABLE 2 Treatment of 1369 Patients* with Peptic Ulcer Admitted to Veterans Administration Hospitals (Branch No. 1) from July 1, 1946 to July 1, 1948

TREATMENT	NO OF PROCEDURES	NO OF DEATHS	MORTALITY %
Gastric resection	226	7	3.0
Gastrotomies	22	0	
Repair of perforations	57	1	1.7
Major gastroenterostomy	5	0	
Others	549	8	
Total			2.3

*These 316 (22 per cent) were operated on.

quality for acute perforation is exceptionally low, the over-all mortality is most gratifying. An interest in research is characteristic of good hospitals and to a certain extent is a reflection of standards. It is significant that two papers from Veterans Administration hospitals were presented at this meeting yesterday. To date, five papers have been published from the surgical services of the four affiliated hospitals. An additional fifteen papers covering a wide range of topics are in process of publication. Recently funds have become available for laboratory studies and special projects so that the future should see a considerable amount of valuable research done in these institutions.

From the foregoing, it is obvious that the surgical standards and standards of the affiliated Veterans Administration hospitals are excellent for training

residents if the variety and volume of clinical material are adequate. There is an unusual number of rare and interesting cases, a steady flow of the simpler types of surgery and an abundance of gastric and vascular work. The amount and type of material available in general surgery is indicated in Table 3, which lists the operations performed by the chief residents in one month in two different hospitals. Similar data could be produced for the subspecialties of urology and orthopedics, which are well represented in the majority of the Veterans Administration hospitals. Finally, there is ample material for training in roentgenology and pathology. Unfortunately, however, the restriction of the clinical material largely to one sex and certain age groups makes it essential for each resident to obtain a part of his training elsewhere. Despite this drawback, an increasingly larger number of able young men are seeking residencies in these

TABLE 3 Operations Performed by Chief Residents in a One-Month Period in Two Veterans Administration Hospitals

HOSPITAL NO 1 OPERATIONS	NO	HOSPITAL NO 2 OPERATIONS	NO
Gastrectomy	2	Gastrectomy	4
Colectomy	1	Colectomy	1
Colostomy	1	Colostomy	1
Cholecystectomy	1	Cholecystectomy	2
Thyroidectomy	2	Lobectomy	2
Appendectomy	4	Appendectomy	2
Herniorrhaphy	12	Herniorrhaphy	3
Lumbar sympathectomy	1	Miscellaneous major procedures	10
Lumbodorsal sympathectomy	1	Miscellaneous minor procedures	16
Miscellaneous major procedures	8		
Miscellaneous minor procedures	25		
Totals	58		41

hospitals and a means of providing them with a balanced training through affiliation of the Veterans Administration hospitals with civilian institutions is highly desirable. The Dartmouth Dean's Committee has taken the lead in this respect by establishing a unified residency between the Hitchcock Hospital and the Veterans Administration Hospital at White River Junction. All their residents are now assured a three-year graded service, which includes work at both hospitals. It is urgently hoped that other institutions will see fit to do likewise.

The large volume of excellent teaching material in the Veterans Administration hospitals makes them especially suitable for affiliation with well staffed community hospitals that may not have large ward services. It is sincerely hoped that under the supervision of the universities affiliations can be established between outstanding community hospitals and the Veterans Administration hospitals that are not, at present, associated with medical schools. Unless this can be worked out, the future of the nonaffiliated Veterans Administration hospital is an unhappy one.

The wisdom of linking the Veterans Administration hospital to the medical schools is shown by the present plight of the nonaffiliated hospital at Togus, Maine. The clinical material in this hospital is comparable to that in any of the affiliated hospitals. The full-time Chief of Surgery is well trained, competent and conscientious, and there are a number of able consultants who visit the hospital regularly. A well conceived program of lectures, ward rounds and clinics is established, but because the institution is not a dean's committee hospital it is not authorized to appoint interns or residents. Consequently, the members of the regular full-time staff are overwhelmed in providing the elementary details of good care. Naturally, it is difficult to keep an able staff in such circumstances. The present chief of surgery remains because it is hoped that sooner or later a residency-training program can be instituted. If he should leave, it would be difficult to persuade a well trained and competent surgeon familiar with the situation to succeed him.

The future of the hospital at Togus and other hospitals to be set up in this branch is dependent upon an affiliation with one or more of the universities. Geographic proximity, although desirable, would not be essential. The moment a hospital is authorized for resident training, defects in the full-time staffs can be corrected because well trained men are willing to take positions in dean's committee hospitals. An able resident staff could then be appointed, and in a very short time the atmosphere and standards of these hospitals would compare with those of the other affiliated hospitals.

If one excludes the nonaffiliated hospitals from the discussion, it is evident that the reorganized department of medicine and surgery in the Veterans Administration has fulfilled expectations. It has attracted distinguished staffs, offers excellent opportunities for training and research, and provides the veteran with the highest quality of care. It deserves a continued and expanding support from the universities and the medical profession.

On the other hand, it would be a mistake to conclude that the notable achievements of the Veterans Administration hospitals are examples on a small scale of what a system of socialized medicine could do for the country as a whole. The record of the Department of Medicine and Surgery has been made despite the fact that it is a governmental system and not because of it. From the very beginning of the new regime, General Paul R. Hawley with the approval of General Bradley insisted that the "red tape" of administrative details be reduced to a minimum and that nothing should hamper the professional personnel in their work. Despite the fact that this policy, vigorously supported by Mr. Gray and Dr. Magnuson, has permeated the entire organization there is a constant struggle between the professional personnel and the Frankenstein of any governmental system.

Thus, elaborate checks and safeguards must control the spending of money that belongs to people of the United States. A new budget must be approved each year by Congress and shared with other departments. It may be exceeded before the end of the fiscal year and sudden precipitate reductions in personnel and travel may occur. Although doctors and nurses are not affected by unique rules and regulations of civil-service employees may shift key technicians or secretaries to other positions and replace them with less suitable people. Moreover, someone must be accountable for the property of the United States Government and despite every effort to minimize it some of the responsibility falls on the shoulders of the professional staff. The financial department requires consultants and attendants to sign in and out and cannot conceive of a doctor visiting a hospital for other than personal remuneration. Personnel ceilings, as well as a forty-hour week for each employee, place a serious limitation on the work that can be done in the operating room. There are also intended building regulations, which if literally interpreted may create the most preposterous conditions. In one hospital the use of a badly needed autoclave was delayed for more than a year because of an apparent lack of authority to make a hole through a wall.

Since these are Government hospitals it is essential for the managers to have more authority than the director of a civilian hospital. They are the sense the director and the hospital trustees. In one branch have been well chosen, and excellent relations between them and their service chiefs have developed. But there are potentialities for discord, and should a manager prove to be dictatorial and unsympathetic with the aims of the professional services, he could make the lives of his service chiefs miserable. Moreover, it would take time to untangle such a situation. Furthermore, both managers and professional chiefs are subject to the unintended influence of Congressmen and service organizations who with the best of intentions may unwittingly interfere with the care of patients. At all, even the consultants, because there is a lack of governmental authority in their suggestions at times may be more confusing than helpful.

These are not criticisms of the Veterans Administration. These are facts that, so far as it is humanly possible, the medical director of the Veterans Administration and his department chiefs have endeavored to eliminate. In this connection it should be stated parenthetically that if the Department of Medicine and Surgery had its own budget under the direction of the Chief Medical Director, a great many of the administrative difficulties that beset the hospitals could be eliminated. But the best of governmental systems is hard to correct. It requires constant and determined resistance.

It takes a strong, patient and selfless man to a permanent position as chief of surgery in the Administration. As long as the organization is comparatively small and administrators like Dr. Hawley and Dr. Magnuson remain at the helm and as long as the universities continue their

support, it is hoped that enough able men will be found for these positions to assure the high standards of care that Elliott Cutler envisioned. To expand this system to all the people would be disastrous. The machine would control the men, and the care of patients would be in the grip of an automaton.

ARACHNIDISM*

Effect of Calcium Gluconate in Six Cases

WILLIAM E. R. GREER, M.D.†

BOSTON

ARACHNIDISM, the syndrome following the bite of a black-widow spider, is a definite clinical entity in the field of general medicine. The bite of the spider *Latrodectus mactans*, found in all but seven states in America, is poisonous. It has been recognized for centuries.¹ Bequaert's² review of the literature in 1926 threw much skepticism attached to the fact that such a creature could, by its bite, produce terrifying generalized symptoms in man. He reported 380 deaths in 17 states in eighteen states. It remained until Blair,³ in 1933, to dispel all doubt concerning the seriousness of this arachnid menace to man. He described the clinical syndrome that follows the bite of a female *L. mactans* after application of the spider to his own finger.

The distribution of *L. mactans* in the United States is wide; this spider has been found in California, Nevada, Arizona, Utah, Colorado, New Mexico, Kansas, Oklahoma, Texas, Arkansas, Louisiana, Mississippi, Alabama, Georgia, Florida, Tennessee, North Carolina, South Carolina, Kentucky, Virginia, West Virginia, Maryland, Delaware, Pennsylvania, New York, Massachusetts (Cape Cod and New Hampshire, among other states). Blair et al.⁴ reported that the black-widow spider is greatly increasing in numbers and invading the large cities. These spiders are found in great numbers in the vicinity of human habitations, not only in outdoor privies, as was formerly believed, but also in beds, garages, automobiles and even high in office buildings.⁵

Although limited in practical application to areas where this spider is indigenous, knowledge of its clinical entity is important since many spider bites are subjected to needless operations because the symptoms often simulate acute surgical lesions of the abdomen. Almost every article in the literature concerning the acute abdomen includes

arachnidism to be considered in the differential diagnosis. If excruciating abdominal pain overshadows the rest of the syndrome surgical operation is often accomplished. An appalling record of human suffering has been checked back to *L. mactans* and its prototypes.⁶

The cases of arachnidism reported represent but a small fraction of the actual number that have occurred; many other cases noted by personal communications are never published. The arachnid menace is more extensive than one would expect. Its curtailment in an indigenous area can only be accomplished by unified efforts of mankind and parasitic enemy insects of the black-widow spider.

Evidence for the incidence of arachnidism rests largely on the statement of patients who have been bitten describing the insect answering the description of *L. mactans*. In other cases observers or the victim have caught the spider and brought it to proper authority to be identified.

In spite of the prevalence of the black-widow spider throughout North, Central and South America and especially in the southern half of the United States, relatively incomplete knowledge existed concerning its life history until the work of Blair.⁷ The species *L. mactans* have been found in dark corners and in clothes closets. They are cannibalistic, feeding on each other whenever the opportunity presents itself. The nickname "black widow" given to the female of the species arises from its habit of capturing and feeding on the much smaller male after he has served the ends of species preservation.

The globose abdomen of the female stands out like a highly polished black pearl. It is attached by a slender pedicle to the smaller cephalothorax. The body averages 1.27 cm. in length. The abdomen is about 0.9 cm. in length. Slender pointed legs when expanded have a span of 3.8 to 5.1 cm. Legs and body are a glossy black and are covered by short, black hairs. On the ventral surface of the abdomen there is a rich red marking resembling an hourglass. Dorsal to the spinnerets in the midline of the convex

* From the Robert Dawson Evans Memorial Massachusetts Memorial Hospital and the Department of Medicine, Boston University School of Medicine.

† Director in Medicine, Boston University School of Medicine, Residency in Medicine, Robert Dawson Evans Memorial Massachusetts Memorial Hospital.

surface of the abdomen is an additional red marking

The full-grown female, particularly when distended with eggs, appears from experiments with animals to be the most poisonous. It is, however, a timid creature and when disturbed makes every effort to escape, this explains the relatively few bites in spite of the prevalence of this arachnid. When cornered or compressed, as between skin and clothing, the spider bites in self-defense. The male is ignored as an etiologic factor of any importance because of its size, timidity and scarcity.

The potent nature of the venom is readily appreciated when one sees a victim of the black-widow spider about an hour after a bite. The victim writhes in agony, terror-stricken, and expressing

the clinical picture into three stages: the stage of lymphatic absorption of the injected venom, characterized chiefly by pains in the bitten area and absence of systemic effects; the stage of vascular dissemination, characterized, clinically, by the explosive onset of widespread agonizing muscular pains and a condition of profound shock depending on the quantity of the venom or its toxic products; and the stage of elimination of the venom or its toxic products, characterized clinically by hypertension, diaphoresis, gradually diminishing muscular pain and evidence of renal damage — this stage is suggestive of an acute toxic nephritis.

REVIEW OF CASES

The syndrome, as presented by 6 patients bitten by the black-widow spider observed in a seven-day period in an overseas tropical area, usually followed a similar pattern: transient excruciating local pain at the site of the spider bite, rapid local edema and redness of the skin at the site — in 2 cases the site could not be identified, in ten to fifteen minutes a "burning sensation" that spread centrifugally from the site of the bite and soon involved the whole body, passing off in about twenty to thirty minutes; a sudden abdominal pain, often cramp-like as in an acute surgical condition of the abdomen, cramp-like pains in the legs, arms and back, a general feeling of "utter weakness", restlessness and extreme fear reaction, often hysteria, headache, nausea and vomiting, and burning of the soles of the feet (in unknown types of bites this symptom may be pathognomonic).

In children there may be convulsions, which are extremely difficult to control.¹¹ Other possible symptoms are variable such as paralysis, cyanosis, dyspnea and urinary retention.

Physical examination in this series revealed the following: the site of injection usually showed an area of erythema with mild edema (in 2 cases the site was not evident), a board-like abdomen, non-tender to palpation, was present in all cases, there was hypersensitivity of the skin, the calf muscles were tender to palpation, 2 patients were in profound shock with blood pressure unobtainable (the other 4 patients had normal or slightly elevated blood pressures), motion of extremities was limited by muscle spasm, and flexion was a prominent feature, the temperature was normal or only slightly elevated, the pulse was slow, being 80 or under in all cases, examination of the blood showed a moderate leukocytosis, and the 2 patients presenting a picture of profound shock showed albuminuria.

The victims all gave an excellent history, and in all cases the spider was identified. One patient described his episode as follows:

I was putting on my shirt this morning when I felt as if someone had stuck a needle in my shoulder. When I tore off my shirt a black spider with a red-orange spot on its belly fell out. The place stung for about 10 minutes,

TABLE 1 Effects of Spontaneous or Induced Stinging of Guinea Pigs by Spiders *

SPECIES	NO OF EXPERIMENTS	NO OF ANIMALS STUNG	NO OF ANIMALS WITH SYMPTOMS		NO OF DEATHS
			LOCAL	GENERAL	
<i>Loxosceles laeta</i>	75	28	28	0	0
<i>Dysdera maxima</i>	50	7	3	4	4
<i>Metozysia dubia</i>	20	0	—	—	—
<i>Cleocnemis junior</i>	23	0	—	—	—
<i>Migala</i>	3	3	3	3	3
<i>Zilla x-notata</i>	30	2	0	0	0
<i>Theraphosid</i>	12	9	0	9	9
<i>L. mactans</i>	25	18	3	18	14

Adapted from Macchiavello.

fears of death. Thesing⁵ states that the venom of the female of this species is fifteen times as potent as that of a rattlesnake. The venom has been stated to be a toxalbumin with its most damaging activity on nerve endings. It is a thick, translucent, oily, lemon yellow-colored fluid, acid in reaction, from which a hemolysin and arachnolysin have been isolated.⁸ A report by Macchiavello,⁹ showing the results of spontaneous or induced stinging of guinea pigs by spiders, is indicative of the formidable nature of *L. mactans* (Table 1). The bite of the *L. mactans* produced the same nervous symptoms in the guinea pig as it did in man, death occurring between four and eighteen hours.

Other authors cited by Blair³ have found similar results in experiments with warm-blooded animals. Experimental studies by Blair showed marked reactions in mice, rats, guinea pigs and chickens. In mice the mortality was practically 100 per cent. Rabbits, cats, dogs and sheep seemed little affected. Baerg¹⁰ gave experimental evidence when, on July 9, 1922, after several attempts, he induced a black-widow spider to bite his finger for about five seconds, sharp pain in the finger and hand being the most prominent symptom, followed by aching pains in the muscles of the lumbar region, shoulders, chest and legs.

It was Blair,³ in 1933, who allowed a black-widow spider to bite him in an experimental study and recorded careful clinical observations dividing

and then a burning sensation spread all over my arm and soon over my whole body. I began to get stomach cramps and my legs ached. Soon I felt weak and dizzy and wanted to sleep but headache and a feeling of terrible nausea came over me.

The patients in this series were immediately given 10 cc of 10 per cent calcium gluconate intravenously. Subsequently they were given a saline infusion containing 10 cc of 10 per cent calcium gluconate. An ice bag was applied to the affected area. Relief was obtained in a short time in all cases and was followed by profound sleep. The patients were out of bed the next day and back to duty on the fourth day. Even the 2 patients in profound shock responded. No morphine was used, and antivenin was not available.

DISCUSSION

The venom has previously been reported to have injurious effects on the isolated heart of the frog.¹² Billman⁸ reported a case with suggestive changes in the electrocardiographic tracing and recommended that more emphasis be placed on the cardiac status in arachnidism. Precordial and epigastric oppression are not uncommon. Bradycardia has frequently been noted by other observers.^{2, 13, 14} In this series normal pulse rate or bradycardia was common.

Blair³ believes that the condition of shock, characteristic of the second stage, suggests the presence of a histamine-like substance in the spider venom. Such a possibility is enhanced by the secretagogue action, evidence of contraction of the bronchial and intestinal musculature and symptoms of acute prostration noted in animal experiments. Indeed, Essex and Markowitz¹⁵ observed certain histamine-like properties of another secretion, crotalin (rattlesnake venom), in experimental studies.

The clinical picture of the development of an acute toxic nephritis has caused much speculation. Other observers¹¹ considered the syndrome to be like hypertension in the adult and eclampsia in the child (children often have convulsions in arachnidism). Four of the 29 cases reported by Walsh and Morgan¹² and 2 of this series showed albuminuria. These findings may be similar to the "allergic nephritis" seen after bee stings.¹⁶

Another clinical syndrome noted in arachnid poisoning is cutaneous arachnidism, or the gangrenous spot of Chile.⁹ Three types of arachnidism have been noted in Chile: nervous arachnidism, produced by the poison of *L. mactans*, cutaneous arachnidism or gangrenous spot, caused by the spider *Loxosceles laeta*, which injects a local necrotizing poison, and viscerocutaneous arachnidism, the intermediate type, in which the patients, in addition to cutaneous signs, showed symptoms of hepatitis with jaundice, hematuria, fever and slight nervous disorders. *L. laeta* is a house spider. There is often a painless latent period after the bite of the black-widow spider, but this never occurs with cutaneous arachnidism. There is absence of general

symptoms in the "gangrenous spot of Chile," but the local necrotizing lesions are severe. The bite is followed by immediate changes in the surrounding epidermis, with blister formation, rupture and gangrenous area. The eschar sloughs, and a superficial ulcer forms and heals slowly.

TREATMENT

About sixty preparations have been used in the treatment of arachnidism. Alcohol seems to be contraindicated, and fatal results have been reported from this agent.¹¹ Strychnine used to be given, and sedatives seemed the most rational treatment in former years. Intravenous magnesium sulfate until symptoms of spider poisoning have disappeared has long been recommended and seemed rational in cases in which hypertension was a prominent factor. Frawley and Ginsburg¹¹ had good results with magnesium sulfate in 11 cases, with freedom from symptoms in twenty-four hours. Hypertonic glucose has been used with varying results.¹³ Morphine sulfate in heavy dosages has frequently been relied upon for relief by some physicians. The results of Gray's¹⁷ observations with convalescent serum seem to bear out the suggestion that antivenin is developed by the patient recovering from the bite of the black-widow spider. It is reasonable to suppose that it will prevent symptoms or cure spider-bite poisoning. Antivenin (*L. mactans*) is listed in *New and Non-Official Remedies*. It is standardized on the basis of its ability to neutralize the venom of the black-widow spider when the two are injected simultaneously in mice. Bell and Boone¹⁸ reported a single case in 1945 in which they regarded neostigmine methyl sulfate as an apparent specific treatment for arachnidism. This article stimulated much adverse comment from other observers, since much time and many other remedies had been given before neostigmine methyl sulfate therapy was instituted. It remained for Gilbert and Stewart¹⁹ to propose calcium salts as a very effective method of therapy. They reviewed previous therapeutic measures in the treatment of arachnidism and presented 5 cases in which intravenous solution of 10 per cent calcium gluconate gave instant and prolonged relief of pain and also produced relaxation of muscular spasm. The intramuscular route was recommended in children, with almost immediate relief. Calcium lactate was ineffective orally, probably because of its incomplete and slow absorption. Calcium chloride is not recommended because of its possible necrotic action on tissues. In the series reported in this article intravenous calcium gluconate was found to give immediate and prolonged relief of muscle spasm and pain in all cases, and it is believed that this is the best available therapy in conjunction with other supportive measures. Others have remarked on the relief given by frequent hot baths.^{2, 10} In Russia hot baths are often used in the treatment

of spider bite due to the "Karakurt," a closely allied species Finlayson²⁰ believes that tetanus antitoxin should be used in all cases

SUMMARY

Arachnidism, a definite clinical entity in medicine, is reviewed, and 6 cases successfully treated with intravenous injection of calcium gluconate are discussed

Arachnidism should be considered in indigenous areas in the differential diagnosis of the acute surgical abdomen. It may simulate appendicitis, perforated viscus, peritonitis or any other acute surgical emergency

The syndrome following the bite of *Latrodectus mactans* may give symptoms referable to many systems of the body. Nervous, cardiac, renal, pulmonary and cutaneous manifestations may be present

Burning of the soles of the feet may be pathognomonic in arachnidism

One should be familiar with the clinical picture so that proper diagnosis is made and proper therapy instituted with avoidance of unnecessary surgical operations

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PERFORATION OF INFARCTED INTERVENTRICULAR SEPTUM, WITH PARTIAL HEART BLOCK*

LIEUTENANT (J G) RALPH VERNON FORD (MC), U S N †

BOSTON

THIS is the report of an acquired interventricular defect that developed at the site of an infarct high in the septum and was associated with partial heart block and a systolic murmur. In previous comprehensive surveys in 1934 by Sager¹ and in 1943 by Weber² a total of 35 cases of interventricular septal perforations due to infarction were collected. Since that time, 18 additional cases have been reported. Prior to the case reported below there were reports of only 2 cases of infarcted septal perforations with clinically detected conduction disturbances of the heart.

The purpose of this paper is to present a case of perforated infarct of the interventricular septum, to comment on the pathogenesis of the associated conduction disturbance and to review the relevant literature.

CASE REPORT

A 72-year-old woman was admitted to the hospital because of semiconsciousness of 4 hours' duration. Ten years pre-

viously she had suffered an attack of "acute" indigestion associated with substernal pain and dyspnea. Since then there had been no recurrence of these symptoms although she had noticed swelling of the ankles for the past few months. On the day before admission she suddenly felt weak and vomited, and was forced to return to bed. On the morning of admission she again vomited and returned to bed, and was found several minutes later in a semiconscious state. She was in obvious respiratory distress for the first time. There had been no chest pain.

Physical examination revealed a thin, dehydrated, semiconscious, orthopedic woman. The skin was cold, damp and cyanotic. Examination of the heart showed the rate to be 54 beats per minute, with frequent irregular beats and enlargement to the left and right. A loud systolic murmur was heard at the apex, but no thrill was felt. The liver was slightly enlarged.

The blood pressure was 76/40.

An electrocardiogram (Fig 1) showed second degree heart block, an abnormal form of the ventricular complex (depressed ST segments in Lead 1, elevated ST segments in Leads 2 and 3 and late inversion of the T wave in Lead 3), elevated ST segments in Lead aVF, and depressed ST segments in Lead VI-5 with unusually high T waves in Lead V3,4. These findings were interpreted as evidence of acute posteroseptal myocardial infarction.

The patient failed to improve and died quietly 5 hours after admission.

On post-mortem examination the most striking findings were in the heart. The coronary arteries were markedly calcified. The left coronary artery was widely patent though markedly sclerotic. The right coronary artery at a point

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†Formerly volunteer assistant, Department of Pathology, Peter Bent Brigham Hospital.

3 cm from its origin was obstructed for a distance of 0.5 cm by a dark-purple, moist mass. Microscopical examination revealed that this was not a thrombus but rather an acute exudative reaction within an intima that was the seat of

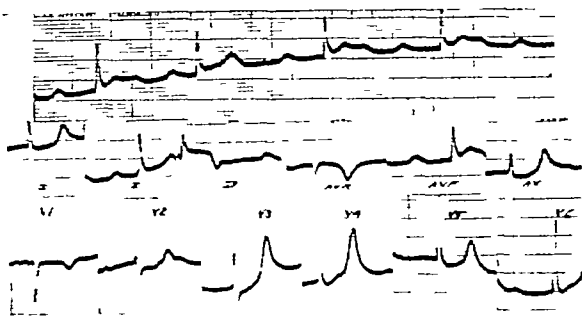


FIGURE 1 *Electrocardiogram, Showing Second-Degree Heart Block (Upper Strip) and Standard and Unipolar Extremity and Precordial Leads Demonstrating Changes of Recent Posteroseptal Myocardial Infarction*

a severe and partially occlusive atheromatous degeneration (Fig 2). The heart was sectioned transversely from the apex to the aortocoronary sulcus at 1-cm intervals. From the junction of the fibrous and muscular portions of the inter-

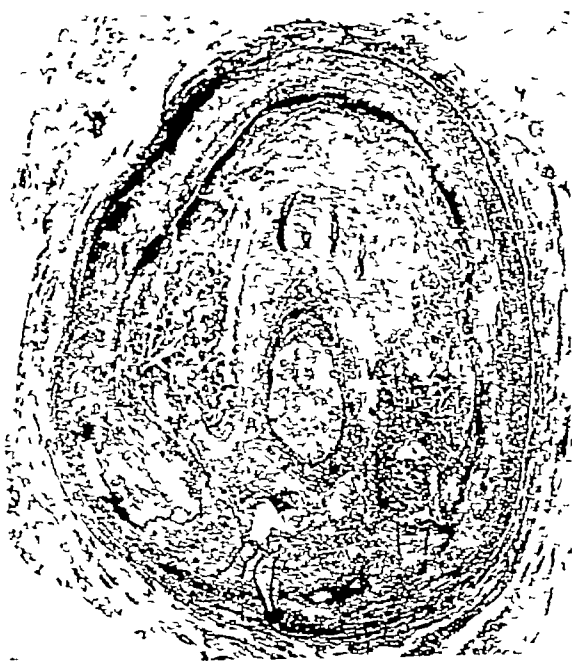


FIGURE 2 *Low-Power Photomicrograph of Coronary Artery, Which Grossly Appeared Occluded*

Note the marked exudate reaction and edema within the wall that is practically occluding the lumen

ventricular septum to a point 3 cm distally, the myocardium was infarcted. Through the middle of this infarcted area there was a fistulous tract, 1 cm in diameter, lined by fibrous material connecting the two ventricles (Fig 3). It is to

be noted that except at the point of perforation of the infarcted septum there was a narrow zone of noninfarcted myocardium immediately beneath the endocardium and beneath the crest of the muscular portion of the septum. Microscopical examination showed changes corresponding to those of myocardial infarction of 48 to 72 hours' duration according to the criteria of Mallory and White.³

DISCUSSION

In general, infarction involving the superior portion of the interventricular septum is likely to produce disturbances of conduction such as auriculoventricular block whereas infarction of the lower apical portion of the septum is more apt to perforate, causing an acquired interventricular

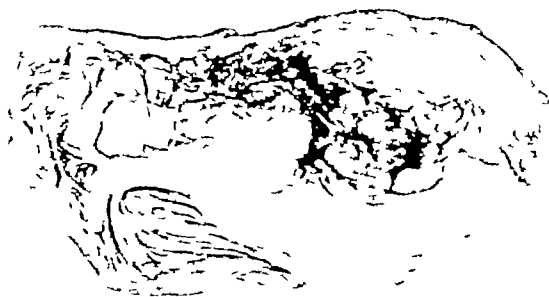


FIGURE 3 *Gross Cross-Section of the Heart near the Base, Showing Perforation through an Infarction of the Posterior Portion of the Interventricular Septum*

septal defect and, characteristically, Roger's murmur. In the case reported above, the perforation of an infarct in the posteroseptal portion of the interventricular septum, with electrocardiographic evidence of second-degree heart block, comprised a situation of unusual rarity and interest. It was noted that the infarction extended to within 1 mm of the crest of the muscular portion of the septum upon which, according to tradition, the auriculoventricular bundle of His rests. After coursing further forward, the bundle of His is said to divide into its two main branches, which then extend downward beneath the endocardium of the muscular septum to the apex. Thus, the location of the infarction and perforation in this case was such as to avoid the bundle branches, but may have involved the main bundle.

REVIEW OF THE LITERATURE

The cases reported by Sager¹ and Weber,² as well as others, were confirmed by post-mortem examination.

In a series of 25,000 autopsies, Edmondson and Hoxie⁴ found 72 cases of cardiac rupture (13 of which were septal) in 865 hearts with recent infarcts.

Wood and Livezey⁵ described the case of a forty-four-year-old man who lived for four years and ten

months after septal perforation following myocardial infarction. This is the longest survival yet reported. It was the sixth case of a septal perforation following a posterior myocardial infarction and only the second case with the associated electrocardiographic finding of right-bundle-branch block.

A case from a clinicopathological conference was presented by Lober and Hertzog⁶ in which an antemortem diagnosis of septal perforation was made.

The patient of Master and Russell⁷ was a forty-seven-year-old man with an acute anterior and posterior myocardial infarction confirmed by the electrocardiogram who developed signs of septal perforation on the third day and died on the eleventh day. Autopsy confirmed these diagnoses and revealed a perforation in the inferior portion of the septum.

Lian's⁸ case of posteroseptal perforation was diagnosed before death and was a remarkable combination of the typical clinical syndrome with electrocardiographic findings of acute posterior myocardial infarction. Analysis of expired air showed a low carbon dioxide content.

Diaz-Rivera and Miller⁹ described 5 cases of cardiac rupture. Only 1 was septal, and it was recognized before death. The patient was a sixty-five-year-old man with typical infarction clinically. On the second day a systolic murmur developed at the cardiac apex and in the third interspace to the left of the sternum. The electrocardiogram showed right-axis deviation, multiple premature contractions and changes consistent with an acute

myocardial infarction. Autopsy confirmed the diagnosis of septal perforation.

SUMMARY

A case of posteroseptal myocardial infarction in which rupture of the septum developed just beneath the "membranous septum" is reported. Electrocardiographic examination shortly before death showed second-degree heart block as well as the characteristic changes of posterior infarction. A loud systolic murmur was heard at the apex, but the patient was not observed long enough for the time of development of the murmur to be established.

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PREMEDICATION IN ANESTHESIA

Unusual Experience with Concurrent Administration of Barbiturate and Pantopon

JAMES C. McCANN, M.D., Ph.D. (SURG)*

WORCESTER, MASSACHUSETTS

THE administration of an anesthetic may be smoothly supplemented or seriously distorted by the use of premedication. The importance of premedication in anesthesia manifests itself in two directions: it has a quieting sedative effect, which renders the patient more amenable to induction, reduces the amount of anesthesia needed for maintenance and prolongs the period of calm following operation, and it manifests side effects, particularly on respiratory activity, which may seriously disrupt the course of anesthesia. The action of the premedicaments in these respects is directly related to tissue susceptibility or idiosyncrasy on the part of the patient.

This report is a consequence of interest in the barbiturates as anesthetic agents that dates back to the use of sodium amytal over fifteen years ago when a report on the use of that agent was published. In that report attention was called particularly to the undesirable side effect of the drug on the respiratory system — pulmonary edema. Four years ago major surgical procedures were undertaken with sodium pentothal administered intravenously as the principal anesthetic agent. A method of supplementing pentothal with trans-incisional novocain nerve block was worked out that established pentothal as a satisfactory anesthetic agent for intravenous injection. This statement is made despite the fact that the use of the agent was undertaken with a critical rather than a favorable bias after the unsatisfactory experience with sodium amytal.

The problem of premedication soon assumed basic importance. Pentothal is directly a depressant of the respiratory center, as are most other anesthetic agents. The depressing action is most marked on the expiratory side of respiration. Pentothal particularly suppresses the reflex stimulation of the expiratory phase of respiration, which results from neurogenic impulses originating in the field of operative trauma. In this respect it tends to restore the reflexly distorted inspiratory-expiratory time ratio from an abnormal 1:4 or 1:6 ratio to a more normal 1:1 ratio. However, pentothal does not exhibit a distinctive effect of both cyclopropane and ether in deeper planes of anesthesia — namely, paradoxical respiration. This effect depends on pharmacologic dissociation of the intercostal and diaphragmatic components of respiration, whereby deep inhalation anesthesia paralyzes the intercostal

component long before there is paralysis of the diaphragmatic component. Pentothal anesthesia, in contrast, when carried too deeply produces concurrent intercostal and diaphragmatic paralysis with the sudden development of apnea. In the light of such pharmacologic facts, the use of premedicating drugs that initially depress the respiratory center calls for careful weighing of their value against the increased depression of the respiratory center by the anesthetic agent.

My experience with intravenous injection of pentothal and trans-incisional nerve block has persuaded me that cautious but effective premedication is a major factor in the successful and satisfactory use of pentothal anesthesia intravenously. The patients are calm, often very drowsy, neurogenic impulses, which reflexly stimulate the respiratory center and influence the rate of utilization of pentothal, are reduced in intensity, induction is more even and quick than it is in the absence of premedication, and the maintenance period requires lesser amounts of pentothal. In view of these apparent facts I have been alert to the problem of synergistic or additive action of opium derivatives used in conjunction with intravenous administration of pentothal anesthesia. The following unusual case, therefore, was considered sufficiently illuminating on this point to merit reporting.

CASE REPORT

A 61-year-old man was referred for surgical treatment of a partially obstructing duodenal ulcer which had not responded to medical treatment. Operation had been planned under continuous pentothal and ether anesthesia with anterior splanchnic block. The patient was given the usual premedication therapy — 0.2 gm (3 gr) of nembutal by mouth the night before operation, 0.1 gm (1½ gr) of nembutal by mouth the morning of the operation, and 0.02 gm (½ gr) of pantopon with 0.0006 gm (1/100 gr) of atropine subcutaneously ½ hour before removal to the operating room. The operation was postponed after premedication had been given because of a reported temperature of 101°F due to an upper respiratory infection. It was later noted that the patient became profoundly drowsy after the medication, with a respiratory rate of less than 10 per minute. After several days, when the cold was better, a posterior gastroenterostomy was performed under the following unusual circumstances. The premedication mentioned above was repeated. Intravenous administration of pentothal had just been started and only 2 cc. of a 1 per cent solution (½ of a grain, a negligible quantity) administered when the anesthetist noted that the respirations were only 5 per minute. The pentothal anesthesia was immediately stopped and no further anesthesia of any kind was administered. The respiratory effort although infrequent was of full amplitude and vigor, and kept the patient in good color. The patient was in deep sleep. The incision was attempted and was continued through all layers of the abdominal wall until the peritoneum was opened. The patient slept soundly with no motor re-

*Surgeon St. Vincent's Hospital.

sponse or objective sign of discomfort from the incision. There was no reflex stimulation of the respiratory center from neurogenic impulses generated by surgical trauma, even from manipulation of the peritoneum such as traction on the stomach. The rectus muscles were relaxed by transincisional novocain block of the intercostal nerves in the sheath. This produced no sensory anesthesia. The anterior splanchnic block was not made, on purpose, the full extent of this unusual drug action being watched for. Intermittent administration of oxygen was carried out. The respirations continued at 5 per minute and were of full amplitude and force on the inspiratory side. Expiration was passive, with no reflex activation of the lateral abdominal muscles as accessory muscles of respiration. There was a long pause, resulting from total respiratory inactivity between expiration and inspiration lasting for about 10 seconds. As the patient's color and condition remained excellent the operation was continued, and a posterior gastroenterostomy performed in a perfectly quiet abdomen.

There was never the slightest evidence of discomfort on the part of the patient. He simply slumbered on. After completion of the anastomosis the abdomen was closed in a routine fashion without the slightest grimace or evidence of discomfort. While the skin was being sutured the patient was shaken sufficiently to arouse him slightly. He was asked whether he had any pain. He shook his head. From then on he made a slight grimace each time the needle was passed through the skin, but nothing else was observed. At the completion of the operation the patient was returned to bed and placed in an oxygen tent. His respirations gradually increased in frequency until they reached 12 per minute by 3 p.m. He became extremely restive at that time and was given 8 mg ($\frac{1}{8}$ gr) of morphine, which immediately depressed his respirations to 10 per minute. He made an easy recovery, being out of bed the following day. He returned home on the 14th day.

Additional observations made on the operating table and during convalescence enhance the interest in but fail to explain this unusual experience. During the course of the operation the patient was rebreathed with oxygen and carbon dioxide (95 and 5 per cent) with an increase in the volume but not in the rate of respiration. He was subsequently rebreathed with pure carbon dioxide for a few seconds, the volume of respiration again increasing and the rate rising from 5 up to 7 per minute. When the pure carbon dioxide was discontinued the rate of respiration immediately dropped back to 5 per minute. The patient was given irritating inhalations of ether fumes to determine if this stimulation would increase the rate of respiration, but it failed to do so. He was given an injection of metrazol and 0.4 mg (1/150 gr) of atropine without stimulating effect on the center, a repeated intravenous injection of metrazol and 0.4 mg of atropine was given, but there was not the slightest increase in either the rate or the depth of respiration, even though the injections stimulated the cerebrum sufficiently to arouse the patient slightly.

During the period of convalescence an attempt to place responsibility for this effect was made by fractionation of the premedication. On one occasion 0.2 gm of nembutal was given at night and 0.1 gm repeated in the morning. The pantopon was withheld. There was no effect other than that of providing a good night's sleep. While the patient was resting in bed the respirations were 16 per minute, and he was quite awake. He was up and about shortly. On another occasion 0.02 gm of pantopon was given in the morning with full precaution to avoid any administration of nembutal the night before. This drug alone had no apparent effect. The patient lay in bed fully awake, with respirations of 16 per minute. On a third occasion the entire premedication routine, with the exception of atropine and pantopon, was repeated with careful watch of the sequence of events. He lay quietly in bed, with respirations normal, awake and complaining because his breakfast was held up. He then received the hypodermic injection of 0.02 gm of pantopon. Over a period of 10 minutes he gradually passed into a state of profound sleep from which he was aroused with difficulty. His respirations dropped steadily during this period to the depressed point of 9 inspirations per minute, and they remained at that level for about 1 hour. They then gradually returned to normal, and the patient was up and about in 4 hours, looking for his breakfast.

DISCUSSION

This experience was apparently a manifestation of unusual combined action by ordinary doses of nembutal and pantopon administered to an adult normal in all respects except for some loss of weight. On the basis of either synergism or additive effect an abnormal suppression of the usual controls of inspiration occurred. On separate occasions combined medication dropped respirations to 5 and 9 per minute. The failure of response to carbon dioxide places the effect on a neurogenic rather than a chemical basis. Failure of response to the pharmacologic stimulation of atropine and the analeptic metrazol indicated the profound depression of the nervous elements in the respiratory center. The absence of reflex neurogenic stimulation from the trauma of surgery was impressive. The phenomena were not in line with the usual action of barbiturates as noted in the administration of intravenous pentothal anesthesia. Barbiturate action tends to normalize the distorted respiration caused reflexly by neurogenic impulses originating in the operative zone. These pain impulses convert expiration from a passive to an active phase characterized by forceful expiratory contractions of the lateral abdominal muscles as accessory muscles of respiration. The expiratory phase of respiration is prolonged by these reflexes, with a distortion of the inspiratory-expiratory time ratio from the normal of 1:1 to an abnormal ratio of 1:4 or 1:6. Barbiturates (pentothal) act on the expiratory component, suppressing the sharp reflex activation of this expiratory phase until the ratio is restored to the quiet, normal 1:1 ratio of the resting state. Beyond this point, there is a reduction in the amplitude and force of respiration by the barbiturates, but usually no alteration of the rate even up to the point of complete apnea.

In contrast with the usual barbiturate action on the expiratory side this experience was one of ineffective inspiratory stimuli that failed to act on the respiratory center in a normal rhythmic fashion. There was a full normal inspiratory effort, followed by passive expiration. There followed a long pause for a resting period of nine or ten seconds. Predicating inspiratory act on the Hering-Breuer reflex, it seems that the threshold for these reflexes had been so elevated by the combined effect of the drugs that it required a summation of stimuli for a period of several seconds finally to achieve sufficient intensity to break over the elevated level of the threshold and create an effective inspiratory impulse. This is more in line with the action of the opiates, so that responsibility for this picture may be ascribed more to the pantopon than the barbiturates.

Undoubtedly, the reduced metabolism at sixty-one years of age contributed to this occurrence. As phenomenal as the depressing effect of these

drugs on the respiratory center was the interruption of the pain pathways to consciousness as a result of which a major operation on the upper abdomen was easily and comfortably performed without benefit of any other anesthetic agent. Administered separately, the drugs displayed no unusual effect. Administered concurrently, they exhibited a remarkable enhancement of pharmacologic effect in three directions: profound sleep, suggesting maximal barbiturate action on the cortex, interruption of pain sensations, suggesting pantopon and possibly some barbiturate action on the thalamus, and depression of respiration on the inspiratory side, suggesting enhanced pantopon action on the inspiratory neurons of the respiratory center—both intercostal and diaphragmatic.

SUMMARY

An unusual case of a gastroenterostomy performed under the effects of preanesthetic medication alone is reported.

Premedication consisted of 0.2 gm of nembutal, given during the night before operation, 0.1 gm of nembutal, administered on the morning of operation, 0.02 gm of pantopon, and 0.0006 gm of atropine, given half an hour before removal to the operating room.

Besides profound sleep and the absence of reflex response to pain, there was depression of respirations to 5 per minute. The respiratory center could not be stimulated by carbon dioxide in ordinary

concentrations or by atropine, metrazol or irritating ether fumes, it responded feebly to pure carbon dioxide. It did not respond reflexly to the neurogenic stimuli of surgical traumatic origin.

Controlled postoperative observations showed that neither nembutal nor pantopon used separately in the same doses had any comparable action. In combination this profound effect, either synergistic or additive, was elicited on three separate occasions.

The possibility of such potent mutual enhancement of pharmacologic effect by barbiturate and opium derivatives administered concurrently prior to anesthesia should be fully recognized even though rarely encountered. This experience also emphasizes the care that should be exercised in the administration of narcotics postoperatively to patients who have received pentothal sodium intravenously during anesthesia.

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CLINICAL NOTE

AN OBSERVATION OF ANTITOXIN TITERS AFTER BOOSTER DOSES OF TETANUS TOXOID*

H J BANTON, M.D.,† AND PAULINE A MILLER, M.S.‡

BOSTON

THE efficacy of tetanus toxoid as an agent for the prevention of clinical tetanus has been well established.^{1, 2} The procedure now most widely employed is to give a basic immunizing course followed by a booster dose at least six months later. Another booster dose is then given in any emergency after an injury that might lead to tetanus infection.

The protection afforded is unquestionably based in large part upon the residual titer of antitoxin persisting after primary immunization and greatly

augmented by routine booster doses. Much stress has also been laid on the capacity of an emergency dose, given after injury, to induce a rapid rise in serum and tissue antitoxin levels. Little information is available, however, regarding the rate at which this rise occurs in human beings. An opportunity arose of plotting the response to a booster dose in 5 members of the staff of the Division of Biologic Laboratories of the Massachusetts Department of Public Health, who received 0.5 cc doses of fluid tetanus toxoid§ subcutaneously in the course of a routine immunization clinic in the Division. All five had previously been immunized with fluid tetanus toxoid either in the Division or while on military duty. The interval in each case since the last injection is shown in Table 1 below. Test bleedings were taken for determination of antitoxin titer just prior to this inoculation, and were repeated from the fourth to the tenth day, inclusive.

This study was undertaken as a result of the joint interest, extending over the past six years, of the Division of Biologic Laboratories and the Department of Bacteriology and Immunology of Harvard Medical School in the preparation, properties and use of tetanus toxoid, and is reported by those re-

*From the Division of Biologic Laboratories, Massachusetts Department of Public Health, and the Department of Bacteriology and Immunology, Harvard Medical School.

†Aided by a grant from the Commonwealth Fund.

‡Assistant director, Division of Biologic Laboratories, Massachusetts Department of Public Health.

§Research assistant, Department of Bacteriology and Immunology, Harvard Medical School.

§The toxoid was prepared in February, 1942, from toxin produced in casein hydrolysate medium by Professor J. Howard Mueller at Harvard Medical School.

sponsible for the clinical and laboratory aspects respectively

The serum antitoxin titers found are presented in Table 1 and Figure 1

only 1 person in 8 whose titer started to rise on the fourth day. This present series follows more closely the immediate changes in titer, by means of daily bleedings

TABLE 1 Antitoxin Titers following Booster Doses of Tetanus Toxoid

SUBJECT	INTERVAL SINCE LAST DOSE OF TOXOID	TITER BEFORE BOOSTER DOSE	TITERS AFTER BOOSTER DOSE						
			AT 4 DAYS	AT 5 DAYS	AT 6 DAYS	AT 7 DAYS	AT 8 DAYS	AT 9 DAYS	AT 10 DAYS
		units/cc	units/cc	units/cc	units/cc	units/cc	units/cc	units/cc	units/cc
G E	1 yr 8 mo	1 0	1 0	> 1 0 < 2 0	2 0	> 2 5 < 5 0	> 7 5 < 10 0	> 10 0 < 12 5	12 5
J A Mc.	2 yr 10 mo	> 0 75 < 1 0	> 1 0 < 2 0	> 1 0 < 2 0	2 0	> 2 5 < 5 0	> 4 0 < 6 0	> 4 0 < 6 0	> 4 0 < 6 0
J M N	1 yr 9 mo	> 0 75 < 1 0	1 0	> 1 0 < 2 0	> 4 0 < 6 0	> 7 5 < 10 0	> 10 0 < 12 5	> 10 0 < 12 5	> 10 0 < 12 5
E R S	5 yr 5 mo	> 0 2 < 0 25	No sample taken	> 0 5 < 0 75	> 2 5 < 5 0	> 7 5 < 10 0	> 12 5 < 15	> 15 < 20	> 15 < 20
H J B	5 yr 8 mo	> 0 025 < 0 05	> 0 025 < 0 05	> 0 1 < 0 25	> 0 5 < 1 0	> 2 0 < 4 0	> 2 5 < 5 0	> 5 0 < 7 5	> 5 0 < 7 5

The person with the highest residual titer had received toxoid the most recently, and conversely the lowest residual titer was coupled with the longest interval

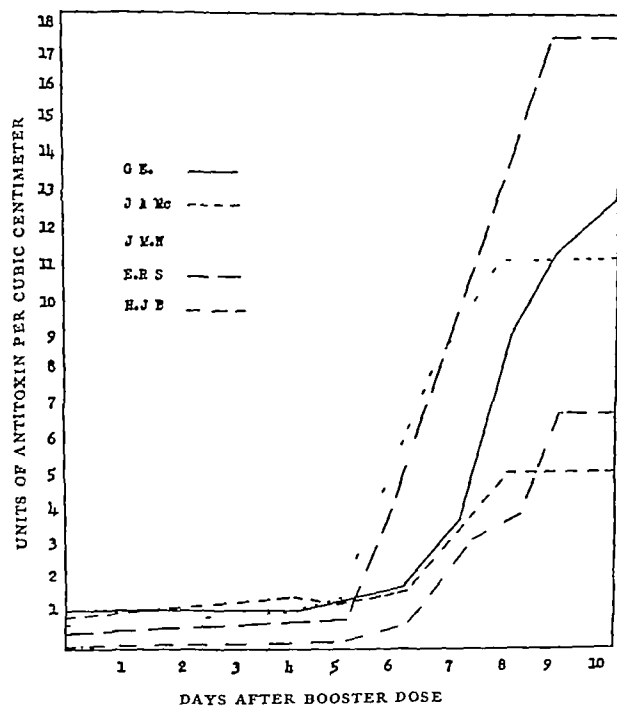


FIGURE 1 Response to Booster Dose of Tetanus Toxoid

None of the titers started to rise before the fifth day, and all were leveled off or appreciably checked by the tenth day. This lag in rise compares with other findings such as those of Gold,³ who found

Since many fatal cases of tetanus terminate within four days of the date of injury, it is apparent from this small number of data that dependence on the booster dose alone after injury may not assure sufficient protection. The residual antitoxin titer resulting from prior immunization may be of greater importance. For adequate protection against tetanus, therefore, it appears that patients should receive periodic maintenance doses as well as the primary immunization, and then receive emergency injections when injured. No set interval for such periodic doses has been established. Evidence suggests that definite protection may persist for as much as five years.^{1,4} In this study the residual titer of 1 subject (H J B) at five years and eight months (Table 1) may have been below the level of adequate protection. Reason suggests, therefore, that periodic booster doses be given for maintenance purposes at intervals of three to four years.

The recent suggestion of a Massachusetts practitioner that physicians in the Commonwealth follow up former servicemen and servicewomen among their patients, and persuade them to have periodic tetanus booster doses, is an excellent one. If this is done a large group of the population can easily be kept immune to tetanus.

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MEDICAL PROGRESS

SURGICAL APPROACH TO CONGENITAL CARDIOVASCULAR DEFECTS*

I M ESSRIG, M D †

NEW ORLEANS, LOUISIANA

PROGRESS in the treatment of congenital cardiovascular defects has been so extensive and spectacular during the past decade that considerable interest has been focused on the entire field of cardiac surgery. In attempting a survey of the surgical approach to the special subdivision of congenital cardiac anomalies, it seems desirable to make a brief review of the older — as well as the new — aspects of general cardiac surgery to evaluate the recent advances more clearly.

HISTORICAL APPROACH

The story of the surgery of the heart is one of the most fascinating in all the annals of medicine, although its development has been relatively slow. This was appreciated in the early days of this century, for Sherman¹ remarked in the annual surgical oration before the American Medical Association in 1902, "The road to the heart is only two or three centimeters in a direct line, but it has taken surgery nearly 2400 years to travel it." (The chest was first opened for empyema in the Hippocratic era.)

Infection

Acute suppurative disease was the first to receive attention,² although many years passed before the suggestions of the pathologists were acted upon by their surgical colleagues. Exactly three hundred years ago Jean Riolan,³ though a staunch Galenist, and a violent opposer of Harvey's new teachings,⁴ advised trephining of the sternum for drainage of the pericardium. A full century passed, deSenac⁵ described pericarditis, recommending drainage for its treatment with the opening in the chest to be made to the left of the sternum in an intercostal space. Still nothing was achieved, and after another half century Desault⁶ and, a few years later, Larry⁷ attempted the procedure, but unfortunately in both instances the diagnosis was in error. Romero,⁸ in Spain, was finally successful in 1819, opening the pericardium for effusion in 3 cases, with 2 patients surviving.

Despite repetition in various countries, the operation did not gain favor, and Billroth⁹ coldly stated, "Parentesis pericardii is a prostitution of the surgical art — possessing more interest for anat-

mists than for surgeons." With this lack of encouragement it took surgeons nearly another century to pass from the pericardium to the epicardium across a space that is such only potentially.

Trauma

Louis Rehn,¹⁰ of Frankfurt, was the first to suture successfully a wound of the heart, and he also was the first to perform decortication for adhesive pericarditis. Moreover, he accomplished a great deal of clinical investigation, and appeared frequently before the profession to defend the infant specialty. For these reasons he might well be considered the father of cardiac surgery. How young this branch of surgery really is can be appreciated by the fact that Rehn died in 1930¹¹ at the age of eighty-one. Interestingly enough, it was in his city of Frankfurt that William Harvey,¹² the discoverer of the circulation, first published (1628) his revolutionary studies on the motion of the heart and blood. To be sure, it was long before Rehn's time that Morgagni¹³ had stressed the danger of compression of the heart from hemorrhage into the pericardial sac, which Rose¹⁴ in 1884 termed "Hertzstamponade." And Block,¹⁵ of Copenhagen, confirmed Morgagni's observations that cardiac wounds were well tolerated and boldly proposed the suture of such wounds as a surgical remedy, having successfully demonstrated its feasibility on rabbits in 1882. Nevertheless, general response was not enthusiastic. Billroth,¹⁶ in the following year — still cold — wrote, "The surgeon who should attempt to suture a wound of the heart would lose the respect of his colleagues." In 1896 Stephen Paget,¹⁷ son of the famous Sir James Paget, stated, in the first work devoted to this subject in English, "Surgery of the heart has probably reached the limits set by Nature to all surgery: no new method and no new discovery can overcome the natural difficulties that attend a wound of the heart."

As if in rebuttal, Rehn,¹⁰ that very year, reported the case of a twenty-two-year-old man with an actively bleeding wound of the right ventricle, which he closed with silk sutures, the patient made an uneventful recovery. This was all the spark that was needed.¹⁸ Within six years, 34 additional operations had been reported. These were reviewed by Sherman¹ in an article that also described his investigations in the use of stay sutures in the ventricle as a method of holding the heart. In 1920 Sir

*From the Department of Surgery, Touro Infirmary, Department of Surgery, Charity Hospital of Louisiana, and the Department of Surgery, Louisiana State University School of Medicine.

†Instructor in surgery, Louisiana State University School of Medicine.

Charles Ballance¹⁹ gave an excellent historical review of the surgical treatment of infectious and traumatic aspects of cardiac disease

Acquired Disease

Billroth²⁰ made another gloomy statement, around 1875, that "those most deeply concerned in the practice of internal medicine make plans for the boldest operations" If the surgical aspect of acquired cardiac disease is divided into three categories—valvular disease, adhesive pericardial disease and myocardial disease—operative intervention in each one was initiated by a bold, clear-thinking, prophetic clinician, each an internist who was to make significant contributions in other fields

Sir Thomas Lauder Brunton,²¹ the discoverer of amyl nitrite, startled the medical profession in 1902 with the suggestion that operative intervention be employed for mitral stenosis, but was uncertain whether the valve should be approached through the auricles or through the ventricles! Vigorous letters, pro and con, but mostly con,²² appeared in the English medical journals Nevertheless, American workers were intrigued by the idea, and pioneer investigative work was launched by W G MacCallum,²³ Harvey Cushing,²⁴ B M Bernheim²⁵ and the late Elliott C Cutler²⁶ Successful operations were reported by Tuffier²⁷ for aortic stenosis, and by Souttar²⁸ for mitral stenosis, both employing digital dilatation of the diseased valve Cutler, Levine and Beck²⁹⁻³⁰ utilized a tenotome knife in 3 cases and then an ingenious instrument—a cardio-valvulotome³¹—to cut stenotic mitral valves in 4 more cases Unfortunately, only the first patient survived Allen and Graham³²⁻³³ perfected a cardioscope with which they could visualize the interior of the heart, but their clinical attempt to use it, as well as Pribram's³⁴ effort, met with failure These experiences resulted in a quietus in surgical intervention for valvular disease until the present time

Brauer,³⁵ who later established the modern concept of thoracoplasty, suggested the procedure of cardiolysis for adhesive pericarditis His proposal gained favor much more quickly than that of Delorme,³⁶ who several years earlier, after careful study of cadavers, had advocated decortication of the heart (He had previously introduced decortication of the lung) Delorme pleaded in vain before various clinical societies in Paris for performance of his operation,³⁷ but it was not until Rehn, doubtful, but still a trail-blazer, performed a decortication for the severer internal form of adhesive disease, concretio pericardii, that the procedure was carried out In 1920, 4 cases were reported with good initial results³⁸

Heberden³⁹ had described what he called "Pectoris Dolor," in 1772, and his contemporary, Jenner,⁴⁰ of vaccination fame, understood its underlying cause Those so afflicted had to suffer almost

another one hundred years before any effective therapy appeared, when Brunton,⁴¹ just a year out of medical school, discovered that amyl nitrite could produce dramatic relief in anginal attacks François-Franck,⁴² known for his sign in patent ductus arteriosus and for cerebral localization, after twenty years of patient research, demonstrated that the sympathetic nervous system has a centripetal function, and that sympathetic ganglions are able to function as reflex centers⁴³ He showed that aortic pain was carried by cervicothoracic sympathetic nerves and in 1899 suggested their resection in angina pectoris An interval of seventeen years elapsed before Jonnesco⁴⁴ first put these ideas to test Daniélopou⁴⁵ and Mandl⁴⁶ also attempted to relieve pain by resection or block of the sympathetic pathways

The next attempt was to reduce the work of the heart by total thyroidectomy,⁴⁷ but this procedure has generally been abandoned⁴⁸

Beck⁴⁹⁻⁵¹ has been the most diligent worker in investigating means to improve the blood supply to the heart He has tried, among other things: chemical irritation of the pericardium—Dakin's solution, silver nitrate, hypertonic saline solution and so forth, foreign-body irritation—gum acacia, horse serum, kaolin and bone powder, myocardial grafts—pericardial fat, pedicle grafts of skeletal muscle from the chest wall, the omentopexy of O'Shaughnessy⁵², and arteriovenous anastomosis (discussed below)

Congenital Defects

The chapter on congenital defects begins with J C Munro,⁵³ who proposed ligation of the patent ductus arteriosus at a meeting of the Philadelphia Academy of Surgery in 1907 This illustrious man was far ahead of his time, although Doyen,⁵⁴ in 1913, unsuccessfully attempted to overcome a congenital pulmonic stenosis with the use of a tenotome In 1937 Strieder⁵⁵ was also unsuccessful in operating upon a patient with patent ductus arteriosus and superimposed subacute bacterial endarteritis

Matas,⁵⁶ in his extensive treatise on cardiovascular surgery, did not even mention congenital defects, and only a decade ago, Levine⁵⁷ stated in his excellent text, "There is no known treatment for congenital heart disease" With timing reminiscent of Rehn, Robert Gross⁵⁸ introduced the present period with the first successful operation for congenital cardiovascular disease, ligating a patent ductus arteriosus in a seven-year-old girl in August, 1938 As might be suspected, one of Billroth's "internists," the child's pediatrician, J P Hubbard, had urged the performance of this procedure

Other leaders of the present decade are Crafoord,⁵⁹ of Stockholm, who first operated for coarctation of the aorta in October, 1944, and Blalock,⁶⁰ who devised the procedure for congenital pulmonary

enosis and first performed this operation in November, 1944. The list of cardiac firsts for this period is so full and varied that objective appraisal is difficult, to say the least.

Two women played a prominent role in laying the spadework for the surgical approach to congenital cardiovascular defects: one, a pediatrician, Helen Taussig, and the other a pathologist, Maude Abbott. Taussig made the suggestion to Blalock that an operation devised to increase the flow of blood to the lungs in cases of pulmonic stenosis would improve the condition of the so-called "blue baby."⁶¹ Her recent monograph on congenital malformations of the heart is a classic.⁶² After encouragement by William Osler, Maude Abbott⁶³ began a collective series of congenital heart lesions, and in 1936 published her atlas of 1000 cases, a milestone in cardiac history. Her efforts, more than anyone else's, provided the stimulus toward present-day interest in the treatment of cardiac anomalies. She devised a clinical classification for congenital heart disease in which patients are divided into three groups.⁶⁴

Group I comprises those without abnormal communications between the right and the left sides of the heart — thus, cyanosis is not a part of the picture. Included are such congenital malformations as simple dextrocardia, pericardial anomalies, pure aortic or mitral stenosis and coarctation of the aorta.

Group II embraces patients with arteriovenous shunt, in whom arterial blood enters the pulmonary circulation. Cyanosis is usually not observed. There is, however, possible transient reversal of flow, with cyanosis. Contained in this group are defects of the interauricular or interventricular septums and patent ductus arteriosus.

Group III includes patients in whom cyanosis is a prominent feature. Among the many causes are defects of the interventricular septum with dextro-position of the aorta, tricuspid stenosis and atresia, transposition of the great vessels, Eisenmenger's complex and the tetralogy of Fallot.

It is exceedingly difficult to estimate the incidence of these major groups or of their components, because of the multiplicity of many defects, as well as the variations that occur with a single lesion, for example, an interauricular defect may be high, low, large, small or primary, or may represent persistence of the foramen ovale and so forth. Nevertheless, it is desirable to have some idea of the approximate range of occurrence, as an aid in orientation, if for no other reason. Since no estimate was noted in the literature surveyed, a list of major defects, admittedly not exact, was compiled on the basis of an analysis of Abbott's cases (Table 1).

EMBRYOLOGIC APPROACH*

Before the conditions amenable to surgery are considered, it is of interest to note the major em-

bryologic implications of congenital cardiac defects. Developmental defects of the heart and great vessels are surprisingly few, considering that the mammalian embryo, having practically no yolk available as food, is dependent upon prompt establishment of relations with the maternal circulation. This entails the necessity of a precocious development of the vascular system of the embryo, for the maternal circulation remains confined within the uterine wall and the embryonic circulation must grow to it.⁶⁵

The heart of the human embryo begins to be formed during the third week of development. Dur-

TABLE 1 *Compilation of Major Defects*

DEFECT	INCIDENCE %
Acyanotic group (approximately 25 per cent)	
Coarctation of aorta	8
Anomalies of aortic arch	2
Aortic stenosis	2
Anomalies of semilunar cusps	5
Pericardial defects	2
Displacements of heart	2
Cyanotic tardive group (approximately 50 per cent)	
Patent ductus arteriosus	15
Defects of auricular septum	20
Defects of ventricular septum	17
Cyanotic group (approximately 25 per cent)	
Tetralogy of Fallot	12
Tricuspid atresia	1
Pure pulmonary stenosis	1
Transposition of great vessels	2
Eisenmenger's complex	5
Persistent truncus arteriosus	1
Complete septal defects (cor triloculare and biloculare)	1

ing the third and fourth weeks the primitive cardiac tube can be seen passing through the pericardial cavity and fixed to the pericardial wall only at its caudal venous entrance and cephalad arterial exit. Since it grows faster than the pericardial cavity, it is bent first in a loop and then in a fallen-S-shaped curve to stay within its boundaries. The proximal arterial end bulges forward and downward, whereas the atrial end pushes behind and above the ventricle. The blood leaves this primitive heart by way of the truncus arteriosus. Later, the truncus separates into aortic and pulmonary trunks. The basis of the partitioning of the heart into right and left sides is largely laid down during the second month of development.

The critical period in the human subject occurs between the fifth and the eighth week — that is, before the cardiac septums are fully formed and while the complex processes of torsion, involution, readjustment and fusion are taking place at the base of the heart, interruption of which is the source of most of the graver anomalies.

If development stops with the pre-septate tubular organ with ventricular bend to the right, the adult fish heart is seen. Similar conditions prevail in the amphibian heart, except that here subdivision into lateral chambers is suggested. Both are examples of cor biloculare.

*Patten's excellent new text *Human Embryology* was used as a guide for this section.

Further ontogenesis is reflected in the reptilian heart, the ordinary snapping turtle having two completely divided auricles, but only a common ventricle — cor triloculare

Meckel,⁶⁶ the "younger" of that famous family, noted in 1802 the curious manner in which graver cardiac anomalies mirror the hearts of the lower vertebrate orders. Von Rokitsansky⁶⁷ (1875) placed the origin of septal defects in the early weeks of embryonic life, while in 1905 Sir Arthur Keith⁶⁸ showed that persistence of the reptilian bulbus was the main etiologic factor in pulmonary stenosis. Spitzer,⁶⁹ in 1923, crystallized these investigations with his theory that arrest or delay of the clockwise torsion that normally takes place in the tubular heart between the fixed arterial outlet and venous inlet during the process of septation accounts for transposition of the great vessels, inverted ventricles and most of the other anomalies.

ETIOLOGIC APPROACH

The cause of malformations of the heart is not clear. Undoubtedly many factors may affect the development of the embryo, both intrinsic and extrinsic.

Intrinsic Factors

These factors are inherent in the male or female germ plasma prior to fertilization, owing to defects in genes transmitted by the laws of heredity. These defects occur because of the phenomenon of mutation — that is, the occurrence of a change in one of the genes that compose the chromosome thread, becoming reproduced in subsequent generations.

The production of such anomalies is in a sense the most characteristic thing about all living matter, being the property that most basically distinguishes living matter from nonliving and that has allowed protoplasm to develop, in its evolution, all the further peculiarities of the human organism.⁷⁰

Murphy⁷¹ has estimated the occurrence of live-born, malformed offspring to be 1 in 213 births. There is a better than 10 per cent chance that a subsequent pregnancy will eventuate in a malformed infant (1 in 8, or twenty-four times greater than the average incidence). The great influence of intrinsic factors is represented by the fact that Murphy found in families possessing two or more malformed children, the defect in the first-born malformed member duplicated in a subsequent malformed sibling in nearly half the cases. This incidence of 50 per cent also was true of duplication of malformation in distant relatives.

The actual incidence of congenital cardiovascular defects at New Orleans Charity Hospital between 1927-1936 was 1.08 per cent.⁷²

Extrinsic Factors

Therapeutic amounts of radium or roentgen irradiation of the human pelvis during pregnancy are

extremely likely to injure the embryo.⁷³ This injury may be due to breakage or rearrangement of chromosome parts, so-called "translocation," which has been shown to occur when mature germ cells are subjected to radiation. Muller,^{74, 75} recent Nobel prize winner, has estimated that the extrinsic factor — irradiation — produces gene mutations (thus becoming an inherited or intrinsic factor) about one hundred times greater than the frequency of spontaneous mutation. It has also been established that the frequency of induced mutation will be proportional to the total dose of radiation received over an unlimited period — that is, the total amount absorbed. Because most such mutations are recessive many generations may pass before the eventual lethality of the defect appears or "shows." On this basis Muller has calculated, for example, that each atomic bomb falling in a highly populous area would probably kill more people scattered throughout future generations than those killed in the generation immediately affected.

Other mutagenic agents are mustard gas,⁷⁶ carcinogenic agents^{78, 79} and perhaps even cosmic radiation.⁸⁰ The importance of mutational prophyllaxis as related to congenital defects is obvious.¹

Virus infection has likewise been implicated as a major extrinsic factor.⁸¹ Gregg⁸² and Swan⁸³ have definitely shown that German measles in the first two months of pregnancy is associated with an extremely high incidence of congenital cataracts and congenital malformations of the heart, if maternal rubella occurs in the third month of pregnancy there is still a high probability that such defects will occur. After the third month the cardiovascular system is practically completely formed, and there is apparently slight liability of injury to the fetus.

Vitamin deficiency during pregnancy has also been shown to be a factor.⁸⁴

DIAGNOSTIC APPROACH

Taussig⁸⁵ has emphasized the differences in diagnosis of congenital heart disease of infants as compared to adults. The same methods of diagnosis that have proved useful in adult cardiac abnormalities were also applied to infants. This is a serious error. Whereas special characteristics of murmur are of great diagnostic aid in adults, in infancy, although the appearance of a murmur may suggest an abnormality, the heart is too small, the blood pressure too low, and the chest wall too thin for the murmur to be of specific diagnostic aid. The existence of a congenital malformation of the heart is suggested in infants by the detection of unusual murmurs and thrills, by the presence of cyanosis with or without clubbing of the fingers and by alteration in the size or shape or position of the heart.

Accurate diagnosis is frequently made possible by the information derived from physical and x-ray examination, and fluoroscopy. Additional important

aids to diagnosis are angiocardiology — that is, contrast visualization of the heart and great vessels with opaque substances — and physiologic studies of intracardiac pressures, oxygen saturations and calculations of cardiac blood flow. Such measurements are obtained by catheterization of the right side of the heart, including the right auricle and the right ventricle and, when possible, the pulmonary artery. The chief criteria for diagnosis are alterations in oxygen content in one or another of these chambers and alterations in pressures.

Cournand and his associates^{55, 56} have shown that by means of the Fick principle⁵⁷ the volume of flow through these chambers may be estimated. The output is calculated from the difference between the oxygen content of the venous blood and that of the arterial blood, and the total oxygen consumption. It is evident that if the quantity of oxygen that a unit of blood delivers to the tissues (or takes up from the lungs) is known, together with the total quantity of oxygen consumed over a given period, the volume of blood that had been engaged in the exchange of this quantity can be calculated.

For example, by an actual measurement of oxygen in a femoral-artery blood a figure of 20 vol per cent may be obtained. This means that 20 cc of oxygen is present in each 100 cc of arterial blood. After the catheter is known to be in the right auricle by pressure measurement and fluoroscopic check, a blood sample taken from the auricle (mixed venous blood) might show a figure of 15 vol per cent — that is, 15 cc of oxygen per 100 cc of venous blood. In this hypothetical normal subject, the total oxygen used by all the tissues in a minute's time might measure 300 cc. Thus, it is seen that 5 cc of oxygen is taken up by the tissues per 100 cc of blood while at the same time the subject is consuming 300 cc of oxygen per minute, then 300 divided by 5 will give the units of blood in 100 cc flowing from the aorta (the oxygen content being practically the same as that of the femoral artery) to the right auricle, or the total systemic blood flow. In this case there would be 60 units of 100 cc, or 6 liters per minute of blood. In the lungs the same principle holds, with the oxygen, of course, going into the blood, instead of coming out. If the catheter tip is placed in the pulmonary artery a blood sample may be obtained that might show a figure of 15 vol per cent, and that from the femoral artery (which is practically the same as the amount in the pulmonary vein) might again be 20 vol per cent. This would show that 5 cc of oxygen has been added to each 100 cc of blood flowing through the lungs. Then the pulmonary flow in such a case is

$$\frac{300}{20-15} \times 0.1 = 6 \text{ liters per minute}$$

The volume of flow through single, one-directional units may most easily be estimated by calculation

of the difference between the pulmonary and peripheral flows. If the shunt is in both directions more complicated formulas must be used.⁸⁵

By means of such measurements, the anatomic lesions in most cases can be predicted with a great deal of accuracy. Nevertheless, because of the inherent difficulties in making an exact diagnosis and the necessity for the therapeutic team to know as much about each patient's status as is humanly possible, radiographic studies should also be utilized.

Though the technic had previously been described, Robb and Steinberg⁵⁹ placed angiocardiology on a practical basis. The usual procedure is to inject 50 cc of double-strength diodrast as rapidly as possible in an antecubital vein. Multiple exposures are then taken, either manually or by use of special equipment, with the patient in an oblique position so that views will be obtained showing the bolus of opaque material in its passage through the various chambers of the heart, the lesser circuit, the great vessels and any abnormal communications that may be present (Fig 1).

As suggested by Getzoff⁹⁰ we have been having our subjects ingest several tablets of an antihistamine drug a short while before the dye is injected, to minimize allergic reactions. The procedure has been found to have almost no ill effect and has proved extremely valuable in differentiating obscure lesions.^{91, 92}

PATENT DUCTUS ARTERIOSUS

Patent ductus arteriosus, although originally noted by Galen,⁹³ has been known as the ductus Botalli since its alleged description by Botallus⁹⁴ (he was born in 1530). This curious by-play in medical history transpired when a charitable editor inserted an extra anatomic plate in a new system containing Botallus's observations, but long after his death.^{95, 96} Cristie⁹⁷ found that whereas 65 per cent of these vessels are still open at the end of two weeks of extrauterine life, only 1 per cent are patent after one year. It is estimated that there are approximately 20,000 people in this country with a patent ductus arteriosus. In Abbott's⁹⁸ review of 1000 cases, the incidence of patent ductus arteriosus was second only to that of intracardiac septal defects. In this malformation, as in a number of others, there is a curious sex distribution. For some unknown reason the defect is two or three times more common in females than in males.

Munro⁵³ demonstrated the feasibility of operation by performing ligations on newborn cadavers, but he stated that he tried in vain to inspire the pediatrician with his views. There still remains a difference of opinion regarding which cases should be selected for surgery. Taussig⁶² states that in general the prognosis varies with the size of the heart and that in the vast majority of cases the heart is but slightly enlarged. She claims that the out-

look is good, the malformation being compatible with a long and active life

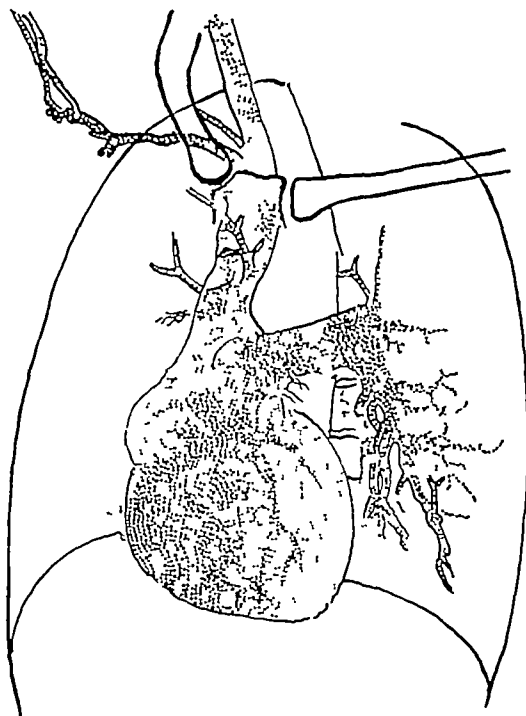
At variance are the statistical data of Abbott,⁹⁸ Bullock et al⁹⁹ and Keys and Shapiro¹⁰⁰ Abbott's mean age of death in 92 cases was twenty-four years (including, however, 20 patients who died in infancy) Bullock and his associates reviewed the cases of 80 patients, all over the age of three years proved by autopsy to have no other significant cardiac anomalies Half the patients died by the age of thirty, and 71 per cent were dead by the age of 40 years, 86 per cent died as a result of the con-

plications intervenes Very few survive once they develop failure (in marked contradistinction to patients with mitral disease)

Von Rokitsansky⁶⁷ showed in 1852 that the direction of flow was from the aorta to the pulmonary arteries This has been confirmed by Eppinger, Burwell and Gross¹⁰¹ who have also demonstrated that the volume of the leak in patients with large shunts constitutes up to 75 per cent of the blood expelled by the left ventricle, and because of this large volume of blood returned to the left ventricle without passing through the right, the output of the



A



B

FIGURE 1 Coarctation of the Aorta — Reproduction and Tracing of Unretouched Angiocardiogram Taken Eight Seconds after Injection of Dye into the Antecubital Vein
The right side of the heart and pulmonary arterial system are visualized

genital lesion — approximately half from bacterial endarteritis, and a fourth from congestive failure Excluding cases in infants and those with cyanosis, the probability that a patent ductus arteriosus will be associated with other significant anomalies is relatively small

Keys and Shapiro¹⁰⁰ analyzed 60 cases in adults (defined as persons over the age of seventeen) and found the life expectancy about half that of the population as a whole — roughly twenty-five years' reduction, or an average age at death of thirty-five years They claim that in the majority of cases the patient's life is fairly normal while it lasts Almost none are cardiac cripples As a rule, they maintain good compensation until one of the com-

left ventricle may be two to four times that of the right

Stunting of growth and underdevelopment are the results of the bypass of a large proportion of the oxygenated output of the left ventricle back into the pulmonary circuit There is a compensator increase in the total volume of circulating blood both plasma volume and red-cell mass,¹⁰² but this is usually inadequate to meet nutritive requirements, although it must be remembered that many persons with a small shunt never have any disability as a result of the abnormality The diastolic pressure is usually low and upon exercise may drop to zero¹⁰³ The pulse pressure is usually wide, depending upon the volume of the shunt These findings

explain why with all but small shunts severe complications are prone to develop. Consequently, it is concluded that an attempt at ligation is justified in practically all cases, regardless of the absence of signs or symptoms of decreased adjustment to the defect.

The optimal time for operation is in childhood since adults are more likely to have less cardiac reserve, and frequently have an extremely short ductus arteriosus, which makes the operation more hazardous.¹⁰⁴ Gross¹⁰⁴ first did a ligation in continuity, and he stated that in children, when the ductus is soft, yielding, elastic and easily compressible, a ligation can almost always be relied upon to produce a permanent closure. In older patients, particularly in those beyond eighteen years of age, the vessel is frequently difficult to compress, and has an exaggerated pulsation transmitted to it by a sclerotic and fixed aorta. In these cases division and ligation, as first reported by Touroff,¹⁰⁵ have given best results.¹⁰⁶ Blalock,¹⁰⁷ who believes that routine division of the ductus arteriosus is an unnecessarily dangerous procedure, employs a method consisting of purse-string sutures at either end of the vessel, a through-and-through mattress suture between and a ligature of umbilical tape over the mattress suture.

Before the duct is tied, it should be compressed manually to be certain there is not an associated hypoplasia or stenosis of either great artery, in which case the ductus arteriosus functions as a necessary physiologic shunt.

Crafoord¹⁰⁸ reports that about half his 71 cases were ligated in continuity and about half divided. He has had only one recurrence (in a case in which the vessel was divided) and now covers the cut ends with a pericardial flap. There have been 2 deaths in his series.

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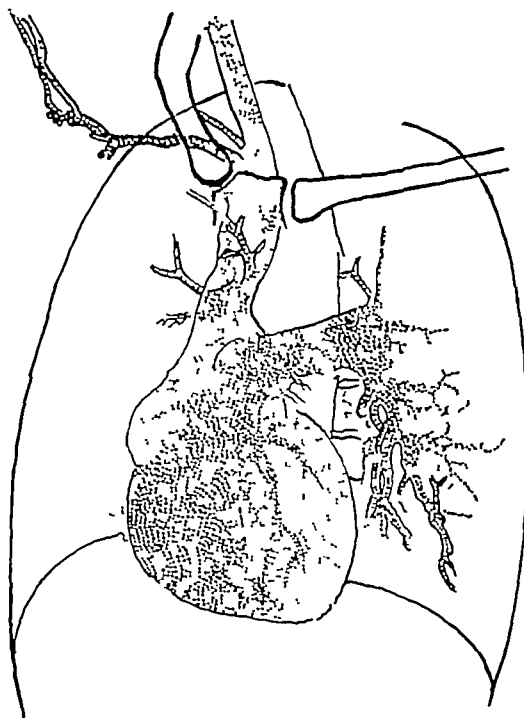
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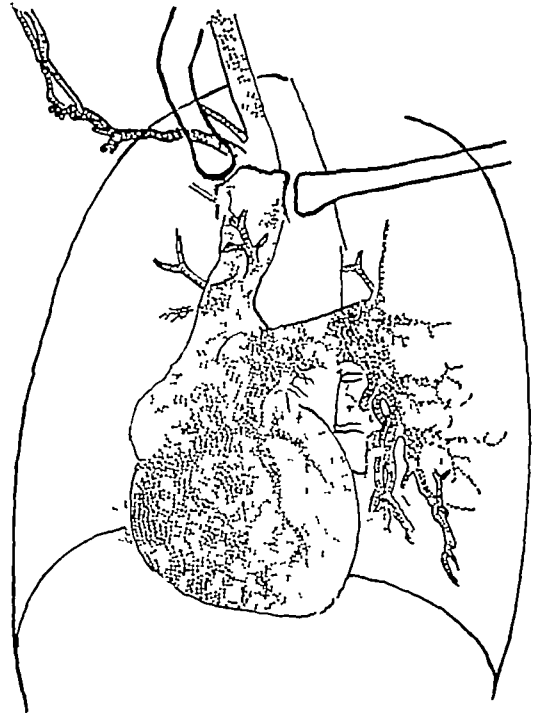
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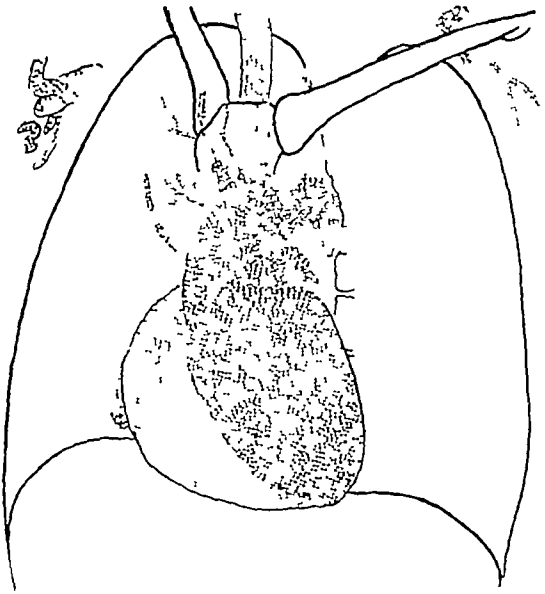
diagnosis will not be made unless there is a careful study of all young patients. Even then the clinical picture may be obscure, and in these cases contrast visualization of the great vessels is an important adjunct in the study of the patient.¹²⁴

The first suggestion of definitive therapy was made by Blalock and Park.¹²⁵ They investigated the feasibility of anastomosing the subclavian artery to the aorta, distal to the constriction, and performed the operation on dogs, suggesting that the left common carotid artery might be a better vessel to use in human beings. Crafoord,¹²⁶ of Stock-

holm, the lateral one, forming a T. The vascularity of the region is tremendously increased, so that blood loss may be great. The aorta is dissected free and the ligamentum arteriosum cut, care being taken to avoid the left vagus and recurrent laryngeal nerve as well as the thoracic duct. After resection of the coarctation, the aorta is anastomosed with either one or two rows of sutures. Either interrupted sutures or a continuous U-suture may be used, the ends being everted so that intima is in contact with intima. The proximal clamp on the aorta must be released gradually over a period of five to six



A



B

FIGURE 2 Same Patient as That in Figure 1

The time is five and a half seconds later. The dye has returned from the lungs and is visible in the left side of the heart, ascending aorta and great vessels of the neck. Note visualization of the coarctation of the aorta and dilated and tortuous subscapular vessels.

holm, reasoned that since the human subject had developed a tolerance to poor aortic blood flow distal to the stenosis, the aorta in these patients could be safely occluded for as long a period as was necessary to excise the stenotic area and do an end-to-end anastomosis. He performed the first two operations, both on male patients, in October, 1944—one twelve years old and the other twenty-seven years old. Both survived.

Gross¹²⁷ independently had arrived at similar conclusions, and he was next to perform the operation in June, 1945. He uses cyclopropane anesthesia and has adopted a posterior thoracic approach through the bed of the fourth rib. Segments of the posterior ends of the third, fifth and sixth ribs are also removed in a vertical incision that connected

minutes to prevent circulatory failure,¹²⁸ since venous return to the heart may be temporarily diminished during the time that the depleted vascular system of the lower portion of the body adjusts itself to its increased blood volume. (Crafoord¹²⁶ states that he has had no difficulty with rapid release of this clamp.)

Clagett¹²⁹ has had to use the procedure originally suggested by Blalock because of technical difficulties, and in a discussion at a recent meeting it was stated that he has employed this procedure on five occasions with 1 death, the ages varied from eighteen to thirty-four years.¹³⁰ In each case severe degrees of aortic sclerosis were noted—a finding important to the thesis that all patients with coarcta-

tion should be operated upon early to obviate degenerative sequelae

Operative intervention is the only definitive treatment, although the not infrequent concomitant finding of congenital intracranial aneurysm (5 to 10 per cent of cases) and bicuspid aortic valves (25 to 40 per cent) militate somewhat against the hopeful results to be expected from surgery. The optimal time for operation is in the second decade.

Below the age of six or seven the aorta is generally too small to work on satisfactorily, and over the age of twenty-five to thirty, it is apt to be sclerotic above the obstruction or thinned out below. Gross¹²¹ reports 40 explorations, of which 35 were resectable. There were 5 deaths. There has been a diminution of hypertension in the upper extremities to normal

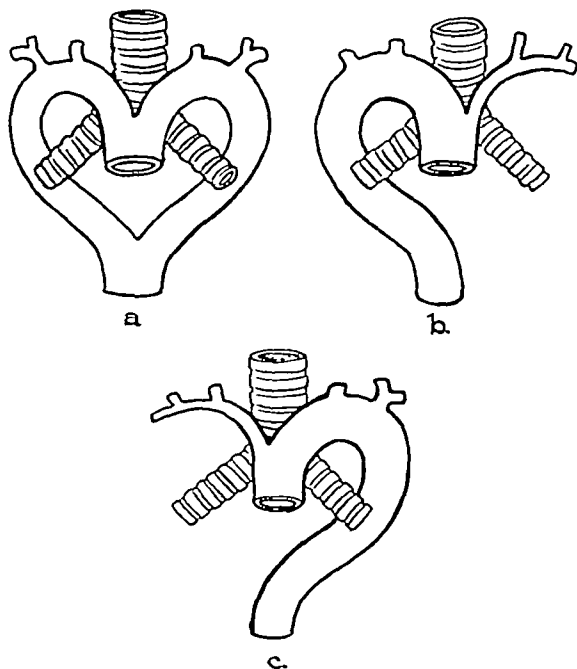


FIGURE 3 Comparative Anatomy of the Aortic Arch

A=retention of primitive double aortic arch—found in frogs, cause of so-called “aortic ring” in human beings. B=retention of right aortic arch, a normal occurrence in birds (seen in approximately 20 per cent of cases of tetralogy of Fallot). C=arching of aorta to the left, the usual occurrence in the human being (many variations of these three basic types of development may be encountered).

in all but one case associated with increase in pulsation and rise in arterial pressure of the leg vessels

PULMONARY STENOSIS AND ATRESIA

Stenosis or atresia of the pulmonary artery was present in 150 of 1000 cases reported by Abbott⁹⁸. About 25 per cent were not associated in the manner described below. The remainder were generally classified as cases of tetralogy of Fallot—that is, pulmonary stenosis or atresia, defect of the inter-

ventricular septum, dextroposition of the aorta (discussed below) and hypertrophy of the right ventricle. This is the most frequently encountered type of congenital cardiovascular defect associated with cyanosis.

Operative experience has led Blalock¹²² to emphasize the fact that in approximately 20 per cent

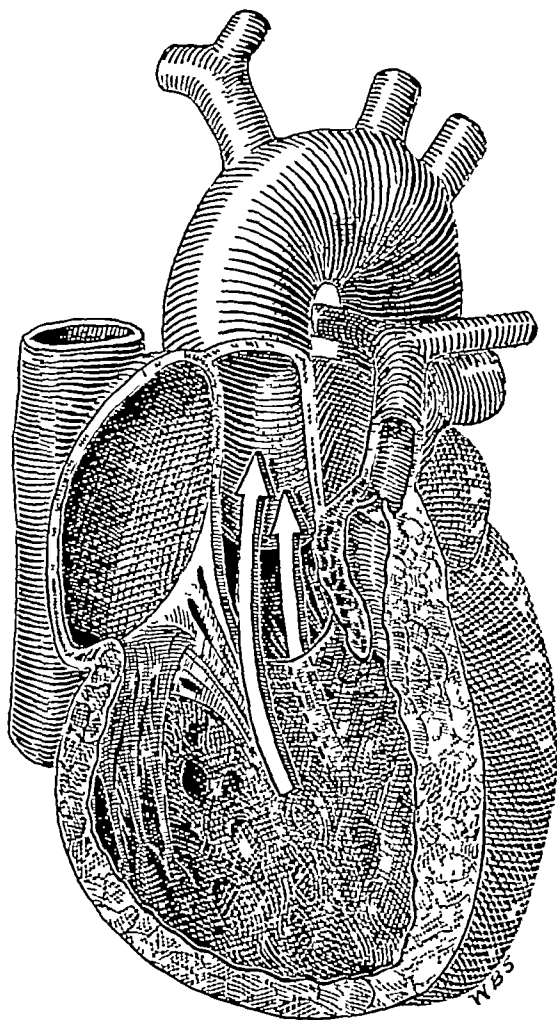


FIGURE 4 Diagrammatic Representation of the Heart in Tetralogy of Fallot, with the Outer Wall of the Right Ventricle Removed

Note the stenosis of the pulmonary artery, interventricular communication, deviation of the aortic orifice to the right and hypertrophy of right ventricle

of operative cases the aorta will be seen arching to the right instead of its usual course to the left, and descending on the right side rather than the left (Fig 3). Thus the aortic arch and descending aorta are dextroposed. This has given rise to an ambiguity in terminology, and, as suggested by Rives,¹²³ it is urged that the orifice of the aorta be referred to as dextroposed when the tetralogy of Fallot is described. As a matter of fact, the fault

lies not with Fallot,¹³⁴ but with his translators, for he was perfectly clear in describing "stenosis of the pulmonary artery, interventricular communication, deviation of the origin of the aorta to the right, and hypertrophy, almost always concentric, of the right ventricle" (Fig 4). Thus, all cases of *la maladie bleue* are associated with a dextroposition of the aortic orifice, only 20 per cent of these patients have a right aortic arch and descending aorta. (This

per 100 cc., and the red-cell count may become as high as 12,000,000.¹³⁷

It was formerly assumed that all the blood that passed through the lungs was not fully oxygenated, so that most investigators believed that a further increase in the circulation of the blood to the lungs would be of no benefit. However, it was observed that the condition of children with pulmonary stenosis and associated patent ductus arteriosus



A



B

FIGURE 5 Unretouched Angiocardiogram in Tetralogy of Fallot

A. Five seconds after injection of the dye, which is concentrated in the superior vena cava and right side of the heart. B. Two and a half seconds later (or the same time as that in Figure 1) instead of entering the pulmonary circulation, most of the flow is shunted through the displaced aortic orifice into the systemic circulation, a small amount is entering the stenotic pulmonary artery.

is the usual occurrence in birds,¹³⁵ and might be referred to as the "bird aorta.")

Although simple defect of the ventricular septum (*maladie de Roger*) is a relatively common congenital anomaly and can be well tolerated, its association with hypoplasia of the pulmonary artery results in a serious clinical syndrome. Instead of the blood flowing through the defect from the left ventricle to the right ventricle, the stenosis obstructs the pulmonary circulation sufficiently to reverse the direction of the flow in the ventricles. Aeration of the resultant small amount of circulating blood in the pulmonary circuit is not sufficient to prevent cyanosis, which occurs in the presence of 5 gm. of reduced hemoglobin per 100 cc. of blood.¹³⁶ The value for the total hemoglobin may become 26 gm.

became worse if the duct was closed, thereby reducing further the flow of blood to the lungs. Consequently, Taussig⁶² proposed that these patients might be improved if a means could be devised whereby a greater volume of blood could reach the lungs.

On the basis of this suggestion, Blalock¹³² devised an operation in which a systemic artery was anastomosed to one of the pulmonary arteries and thus increased the pulmonary flow. Doyen⁶⁴ was the pioneer in this particular location, having attempted in 1913 to divide what was believed to be a stenotic valve with a tenotome knife. The patient died several hours later, and examination revealed the usual finding — namely, that the defect is commonly in the pulmonary conus rather than in the

valve itself (Recent work of Brock is discussed below)

In untreated cases of pulmonary stenosis the life expectancy is only twelve and a half years, with a maximum of about twenty-five years. Chief complications are cardiac failure, poor development, pulmonary tuberculosis, cerebral thrombosis and bacterial endarteritis.

The underlying principle in the choice of patients for operation is that there must be an inadequate flow of blood to the lungs. The two outstanding diagnostic features are roentgenographic evidence that the pulmonary artery is small and clinical and roentgenographic evidence of absence of congestion in the lung fields.

Additional information concerning the pathologic physiology of congenital heart disease has been supplied by Bing et al.¹³³ and by Dexter and his group.⁵³ In employing the method of intravenous catheterization for studying cardiac dynamics, Bing, Vandam and Grav¹³³ have been able to measure the outputs and pressures of the various chambers of the heart, the pulmonary artery and the total pulmonary flow, including that through the collateral channels. This has enabled them to make exact differential diagnoses in difficult cases. Bing states that the three most important indications for surgical creation of an artificial ductus arteriosus are a decrease in effective pulmonary blood flow, a reduction in pulmonary-artery pressure, and a diagnosis of intracardiac shunt. The limitations and potentialities of such methods have been described by Dexter et al.⁵³ Auricular and ventricular septal defects offer greater difficulty in diagnosis. Also of distinct value is visualization of the chambers of the heart and great vessels¹³⁹ (Fig 5) — a procedure just being adopted for routine use in many centers.¹⁴⁰

The preferred age for operation is from five to nine years, since the infant mortality is approximately 30 per cent as compared to one of 10 per cent for children.¹⁴¹ Taussig¹⁴² does not advise operation in those eighteen months and younger, unless the infant is doing very poorly and it appears that the chances of survival to an old age are less than 50 per cent. The early development of attacks of paroxysmal dyspnea is an unfavorable sign. The period of greatest difficulty occurs when the ductus arteriosus is being obliterated — usually between six and eighteen months. As collateral circulation and compensatory polycythemia develop (one to three years) attacks of dyspnea diminish. Most infants who survive until eighteen months of age manage to hold their own for a time, and then begin to improve.

Leeds¹⁴³ showed in dogs that anastomosis of the aorta to the pulmonary artery could be done. Utilizing this approach and by means of an ingenious clamp, which, although reducing the aortic lumen, still allows approximately 50 per cent

flow during its application, Potts et al.^{144, 145} are doing aortic-pulmonary anastomoses. Advantages are that the shunt can be made whatever size is deemed necessary, and that the innominate artery can be conserved in younger patients. At last report they have operated on 41 patients for pulmonary stenosis, 10 below the age of two and three below one year of age. Potts reports 4 deaths in this series.

The anastomosis of the left subclavian artery to the left pulmonary artery is advocated by Holman.¹⁴⁶ Because of sharp angulation of the subclavian artery in 4 cases, he has deliberately divided the left pulmonary artery proximal to the anastomosis, and has noted no subsequent detrimental effects.

Blalock¹⁴⁷ still prefers an end-to-side anastomosis, using the subclavian artery in most patients who are more than two years of age. The desired aim is to choose a systemic artery of such caliber that the polycythemia and cyanosis will disappear but not large enough to place undue strain on the heart. The incision in the chest is usually made on the side opposite to that which the aorta descends (as mentioned above). It is desirable to use the subclavian branch of the innominate rather than the opposite subclavian, which arises directly from the aorta, since the former makes a less acute angle with its parent artery after the anastomosis is performed.

Preoperative studies will have given a good indication of the size of the artery required — the greater the degree of arterial oxygen unsaturation, the larger the vessel that is needed. It has been found that the pressure in the pulmonary artery as determined at the time of operation is generally equivalent to 150 to 240 mm of water. If the pressure is elevated in excess of 300 mm approaching or equaling the aortic pressure, the chances are that there is an absence of the ventricular septum, and the procedure should be canceled since the flow of blood inevitably depends upon the relative pressure between the systemic and pulmonary circulations.¹⁴⁷

If the patient has pronounced polycythemia and if the loss of blood during the operation is minimal, whole blood equal to approximately 1 per cent of the body weight is removed at the conclusion of the operation. It has been found that there need be no concern about the circulation of the arm when the subclavian artery is used, however, when the innominate artery is divided there is danger of cerebral ischemia or thrombosis.

Up to the present time Blalock and his associates have operated upon 415 patients, who were thought to have tetralogy of Fallot. The over-all mortality, including deaths among those in whom an anastomosis could not be performed, those in whom the diagnosis was in error and those who have died since leaving the hospital, has been reduced to 18 per cent. In 283 cases in which the subclavian

artery was used for the shunt the mortality was 10 per cent. On the other hand, when the carotid or innominate artery was utilized,¹³² the rate was approximately 30 per cent. It should be emphasized that surgery is not indicated for cor biloculare or cor triloculare, persistent truncus arteriosus and Eisenmenger's complex — distinguished from the tetralogy of Fallot by a normal or even dilated pulmonary artery.

RECENT DEVELOPMENTS

Some of the remaining anomalies are being ameliorated or remedied by surgical procedures. Others are in the process of investigation in the experimental laboratory.

Gross,¹⁴⁸ in 1945, reported the first successful surgical division of a congenital vascular ring around the trachea.

Tricuspid atresia, until recently considered inoperable,¹⁴⁹ has now come to surgery. Potts and Gibson¹⁵⁰ described 3 patients successfully operated upon with performance of aortic-pulmonary anastomosis. The physical findings in this anomaly are identical with those encountered in the tetralogy of Fallot. Differential features are left-axis deviation in the electrocardiogram (the only lesion that causes cyanosis and has this characteristic) and hypertrophy of the left ventricle and hypoplasia of the right ventricle, which produces a suggestive roentgenographic silhouette.

Shumacker¹⁵¹ has recorded the first case of coarctation of the aorta complicated by a sacular aneurysm just distal to the stenosis successfully treated (February, 1947) by resection of the stenotic area and aneurysm with repair of the aorta by end-to-end anastomosis. Alexander and Byron¹⁵² had a similar case, which was successfully treated by resection alone without anastomosis.

Brock¹⁵³ has recently recorded his experiences with the direct approach of Doyen to the pulmonary valve in cases of pulmonary stenosis. This method was restudied because of his belief that the stenosis is purely valvular or diaphragmatic in a proportion of cases far higher than heretofore supposed. He examined the valves, at operation, by means of a cardioscope inserted through the pulmonary artery, but has decided that this approach is unsatisfactory.

The first patient was operated on in February, 1948. A valvulotome was inserted through an incision in the wall of the right ventricle and used to divide the pulmonary valves. A special dilating forceps was then passed and opened fully in the region of the stenosis. The patient, an eighteen-year-old girl, survived and showed decided improvement subsequently. The procedure has been repeated in 2 more cases, in both of which the patients survived. This operation is not meant to supplant the Blalock procedure, but it does have definite advantages in cases in which the stenosis involves the pulmonary valve itself rather than the pulmo-

nary conus. The exact proportion of such cases will have to be reinvestigated, but this work of Brock's represents another pace-setting advance. (In 155 cases of pulmonary tract anomalies studied by Keith,¹⁵⁴ a defect was found in the pulmonary conus in 133, and in the pulmonary valve alone in 22, he estimated that the pulmonary conus would be involved in 90 per cent of the cases.)

Hanlon and Blalock¹⁵⁵ have recently shown experimentally that anastomosis of the pulmonary vein to the superior vena cava can be done. If feasible in man, this delicate procedure offers a possible approach to the surgical treatment of complete transposition of the aorta and pulmonary artery.

Utilizing the same approach and occlusive clamp, but shifting the operative field slightly distalward, the same workers¹⁵⁶ have been able to obtain an entirely different result — that is, the production of an interatrial septal defect under direct vision, without interruption of the circulation, with minimal loss of blood and with fairly accurate control of size — truly a brilliant achievement. Though he suggested a blind approach through the jugular vein, Jarotzky¹⁵⁷ apparently was the first to recommend such a shunt, knowing that the patient with a mitral stenosis associated with an open foramen ovale (Lutembacher¹⁵⁸ syndrome) has a comparatively good prognosis (forty years¹⁵⁹).

Gibbon and Templeton¹⁶⁰ have recently reconstructed and replaced leaflets of the tricuspid valves with pericardial and venous grafts in dogs.

In the field of myocardial ischemia Beck¹⁶¹ has continued pre-eminent in the search for methods to revascularize the heart. Louis Gross¹⁶² ¹⁶³ made the important discovery that ligation of the coronary sinus produced extensive and abundant dilatation of the intramyocardial collateral channels. Sutton and Lueth¹⁶⁴ found that the pain fibers involved in experimental coronary occlusion are located in the adventitia of the coronary artery. Fauteux¹⁶⁵ combined these last two facts by ligating the magna cordis vein alone (more distal than the coronary sinus) or combined with pericoronary stripping in a total of 15 patients over a six-year period. His results are encouraging.

In view of these advances J. T. Roberts¹⁶⁶ (another internist), suggested to Beck¹⁶¹ the possibility of making an arteriovenous fistula to the heart to increase a deficient blood supply. Utilizing various cannulae¹⁶⁶ as well as the Potts clamp, Beck and his workers have been successful in grafting a systemic artery into the coronary sinus in dogs. They have recently reported the first case (January, 1948) in a human being in which a new connection was made from the aorta to the heart with a transplanted segment of brachial artery. The patient recovered from this extraordinary operation.

Gross and his associates¹⁶⁷ report encouraging early postoperative results after the use of arterial

transplants in the treatment of cardiovascular defects

Polished tubes of a plastic (methyl methacrylate) material containing a movable valve were inserted in the aorta by Campbell¹⁶⁵ in dogs with surgically produced aortic valvular insufficiency. Clotting of blood about the moving valve did not occur for the length of time the animals were observed. The clinical use of such materials, particularly polythene, has a promising future in surgery.¹⁶⁹⁻¹⁷⁰

Smithy et al¹⁷¹⁻¹⁷² are reinvestigating the use of the valvulotome as applied to aortic stenosis. The instrument was first introduced through the aorta, but later work has shown that the wall of the left ventricle offers the most effective approach. This approach was also found best by both Cushing²⁴ and Bernheim²⁵ forty years ago. In those days MacCallum²³ and Allen³² were introducing their valvulotomes and cardioscopes through the left auricular appendage. Cushing reported the first successful attempt to produce valvular lesions of the heart by an intrathoracic approach. He emphasized then that a successful operation must be done on the animal before being attempted on man.

* * *

Some understanding of the surgical approach to cardiovascular disease has become mandatory for the present-day clinician. The recent advances in treatment of pulmonary stenosis, coarctation of the aorta, anomalies of the aortic arch and patent ductus arteriosus are brilliant and promising refinements in the art of surgery. In fact, their diagnosis and treatment are now on a highly scientific plane. The operative treatment of acquired cardiac disease has been reintroduced. Further technical advances are bound to occur. Such intricate and involved procedures call for highly trained and skilled groups of workers — cardiologists, pediatricians, surgeons, anesthetists, roentgenologists, physiologists and probably others. Whether such procedures can or should be done by the average well trained surgeon in the average hospital is doubtful. On the other hand, whether it is economically or socially wise for the patients requiring these procedures to go to special regional centers is also a moot question. Physicians and surgeons should lead the way not only in introducing these new methods but also in discussing and suggesting means to assure their availability to all groups in all regions of the country.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 35011*

PRESENTATION OF CASE

A twenty-two-year-old woman was admitted to the hospital complaining of pain in the left leg.

Ten years before admission, following a fall, she had pain in the lower back for several months. Six weeks before admission she began to notice pain along the anterior aspect of the proximal third of the left lower leg, deep within the muscle group. This leg pain was "wave-like, deep and boring." It was fairly constant and more marked after exercise, but not incapacitating. It did not keep her from sleeping, except to waken her early in the morning. The pain sometimes radiated up the posterior thigh and lower back but never farther distally than the mid-lower leg. In the week before admission she noticed weakness of the left foot when she was tired.

On physical examination the left calf was 0.6 cm. larger than the right, and there was questionable prominence of the head of the left fibula. There was no calf tenderness or sensory change. The muscle power in the foot and ankle was equal bilaterally. There was slight tenderness in the left buttock. The ankle jerks were equal, the knee jerk seemed to be more active on the left.

The blood pressure was 140 systolic, 92 diastolic.

Examination of the blood demonstrated a normal white-cell count, hemoglobin and urine. The sedimentation rate was 4 mm. in one hour. The blood calcium was 9.8 mg., and the phosphorus 4.1 mg. per 100 cc., and the alkaline phosphatase 2.8 units.

X-ray examination of the skull, lumbar spine and pelvis was not remarkable. There was no evidence of bone destruction or alteration of the intervertebral spaces. Examination of the left knee showed no joint abnormalities. There was a small radiolucent area 7 mm. wide and 15 mm. long in the medulla of the proximal third of the fibula. There were one or two small, irregular septums within the lesion, the margin of which was smooth and slightly sclerotic. The overlying cortex was

slightly elevated, but there was no break in the cortex and no periosteal reaction (Fig. 1).

An operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. WILLIAM ELLIOT†: I think we can rule out anything in the spine because of the absence of sensory changes in the leg, muscle weakness and the fact that there is no atrophy. As far as the skull is concerned, I see nothing there that is of interest, and I see nothing remarkable in the dorsal spine.

In consideration of a lesion in the bone we either consciously or subconsciously decide that it is infection or a tumor. In this case I believe we can more or less rule out an infectious process, certainly, it was not an acute infectious process. If it was a tumor, it forces us into a large group of possibilities, and first we must decide whether it was malignant or benign. There is nothing to indicate that this



FIGURE 1

was a malignant tumor. There was no new-bone formation, periosteal proliferation or any of the other stigmas we expect to see in malignant tumor.

As to the other conditions that this may represent, I think we can rule out hyperparathyroidism on the blood chemical findings as reported here. In most of the lesions of hyperparathyroidism that we have encountered there has not been an increase in thickness of the cortex over the lesion. Usually the cortex has been thinned out, and this is also the x-ray finding in fibrous dysplasia and certain

*Presented at a meeting of the New England Cancer Society held at the Massachusetts General Hospital.

†Radiologist, Worcester Memorial Hospital, Worcester, Massachusetts.

other lesions. As I said before, this apparent thickening of the cortex at the site of the lesion is important. There is a condition described by Jaffe and Lichtenstein¹ as nonosteogenic fibroma, which is benign and, to my knowledge, gives no symptoms. It may occur along the shaft of the long bones, and in a case that we have followed over a period of years there was definite thinning of the cortex, but no symptoms referable to the site of the lesion. The nonosteogenic fibromas produce no symptoms and, as a rule, are incidental findings.

Another possibility is a cartilage inclusion, which occurred at the time the line of the epiphysis was at the site of the present lesion, and moved down the shaft with the increase in the length of the bone. Nothing is said about point tenderness — a finding usually present in osteoid osteoma. Whether or not osteoid osteoma is a clinical entity or the result of low-grade infection I will not discuss at this time. I believe this was an osteoid osteoma, and I base this opinion on the fact that these lesions may occur in the medullary cavity against the inner surface of the cortex or within the cortex itself. Pain is the symptom that causes these patients to seek medical advice. Pain, as a rule, is slow in onset, it becomes more aggravated as time goes on, and it may be quite constant. The physical findings are more or less absent except for point tenderness over the lesion itself. Or there may be slight swelling about the lesions, which this patient had. I do not believe this was eosinophilic granuloma because again there is usually bone destruction and a little more reaction about the lesion itself in that condition.

Regarding the operation that this patient had, I believe it was a simple excision of the lesion, with possible preservation of the cortex away from the lesion.

DR GRANTLEY W. TAYLOR: I wonder why Dr. Elliot did not allude to benign giant-cell tumor in that area.

DR ELLIOT: I should have. Benign giant-cell tumor does occur along the shaft. A giant-cell tumor of the size of this lesion would have been asymptomatic, and again there is thinning of the cortex as a rule at the site of the tumor. This cortex was a little elevated and thickened, which I believe is against benign giant-cell tumor.

DR JAMES W. JAMESON: Do you place any significance on the pain occurring at night?

DR ELLIOT: That frequently happens in cases of osteoid osteoma.

DR PHILIP BATCHELDER: Does it have a nidus in the center?

DR ELLIOT: There is a small area of increased density in the cortex, but I cannot be sure that this represents the nidus. I believe Jaffe² states that the nidus may disappear as the lesion matures.

DR GEORGE C. LEVENE: I would agree that from the description this was osteoid osteoma.

DR DOUGLAS J. ROBERTS: Would you consider fibrous dysplasia?

DR ELLIOT: I had considered that. Quite frequently the cortex shows a little thickening and may be bulging, of course, but usually there is a little thinning and not the elevation that this patient had. I think you can see on the films a definite thickening of the cortex as it comes up along there, which



FIGURE 2

I believe is the sclerosis that has been described in the osteoid osteoma.

CLINICAL DIAGNOSIS

Benign tumor

DR ELLIOT'S DIAGNOSIS

Osteoid osteoma

ANATOMICAL DIAGNOSIS

Nonosteogenic fibroma of bone (fibula)

PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN This patient was operated on by Dr Edwin Cave, who resected the lesion in toto. I have some microscopical sections of it, which I will show. The first slide (Fig 2) is a low-power view of the lesion showing cortical



FIGURE 3

bone at the top and a loose fibrous lesion in the medulla. Note the normal fatty marrow around part of the lesion. A higher magnification (Fig 3) shows that the lesion is made up almost entirely of thin, spindle-shaped fibroblasts without any evidence of osteogenesis. In addition, there are a great many cells filled with fat, which are undoubtedly

merely phagocytes. The whole picture fits in exactly with what Jaffe¹ called nonosteogenic fibroma. It is about the second or third case that we have seen here. These tumors, according to Jaffe, do produce occasional symptoms. I do not believe they are all symptomless. They often cause pain and almost always occur in children between the ages of eight and sixteen, usually under twenty in contrast to giant-cell tumor, which occurs almost always above twenty. It is a tumor that in the past has been called a variant of giant-cell tumor. It certainly does not look at all like osteoid osteoma. The lesion is perfectly benign.

DR ELLIOT I thought that the lesions were always incidental findings.

DR CASTLEMAN In his report of 10 cases Jaffe stated that in half there was a history of trauma that apparently attracted attention to the area where the lesion was found by x-ray examination.

DR CLINTON MULLINS How can you differentiate that from a healed osteomyelitis?

DR CASTLEMAN There is no evidence of inflammation at all, and the type of connective-tissue cell is very dense, without any cellular reaction.

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CASE 35012

PRESENTATION OF CASE

A forty-eight-year-old carpenter was transferred from another hospital because of an abdominal-incision dehiscence and draining small-bowel fistula.

The patient had been well and working up until three months before entry, when he began to feel dull, "crampy" pains in the epigastrium, lasting a few minutes. These occurred several times a day and were relieved by two or three glasses of whisky. They were not related to meals. The patient stated that for many months he had often had a desire to defecate without success. Five weeks before admission the pains became more severe and frequent. He stopped work and started drinking as much as a pint of whisky each morning, with little relief of pain but with nausea and vomiting of gastric contents. One week later the pain suddenly became very severe after he had taken a large glass of whisky. He became "pale and dizzy," and his upper abdomen "very hard." He was very weak and drove his car home with great difficulty. His abdomen was painful to touch. The following day he was admitted to another hospital. Physical examination revealed an obese, middle-aged man complaining of upper abdominal pain. His face was flushed and he perspired profusely. His temperature and pulse were normal. The chest was

clear and resonant throughout. The upper part of the abdomen was distended, firm and very tender. The lower part of the abdomen was much softer and not distended. The abdomen was tympanic, and peristaltic movements could not be heard. Repeated enemas gave no results. In the other hospital the patient's temperature remained at 99°F, and the pulse was normal for three days. The distention became greater, and the pain generalized. There was difficulty in breathing. He at no time vomited or felt like vomiting. A Wangensteen tube was introduced, and a large amount of fluid recovered in a twenty-four-hour period. The following day his condition was worse. A diagnosis of retrocecal appendix was made, and a laparotomy done. The large bowel was distended. The intestine showed acute enteritis bordering on a purple color. The appendix was perfectly normal and was removed. A colostomy was performed to relieve the distention. The distention persisted. Three days later a fecal fistula formed about 8 cm above the colostomy opening. There was induration below the colostomy, with questionable abscess formation. Two days later the abscess was drained, and the patient improved. His appetite was better. After a period of two weeks there seemed to be a breaking down of the incision, owing to the fecal fistula and colostomy. The patient was given penicillin and intravenous fluids. Following this he developed dyspnea and marked perspiration. Intravenous fluids were cut down to 500 cc three times a day. He had been taking moderate amounts of fluid and was co-operative at all times. He grew progressively weaker. At no time following operation was there any bowel movement, although repeated enemas were tried. The abdomen remained distended and tympanic. The wound drained constantly and showed no attempt to close. The urine showed a +++ test for albumin, and the sediment contained casts and a few red and white cells. The blood hemoglobin was 90 per cent and the red-cell count 4,590,000. The white-cell count was 7800. Two days after admission the blood sugar was 136, the nonprotein nitrogen 60 and the creatinine 29 mg per 100 cc. Twenty-four hours after operation the nonprotein nitrogen was 39 mg per 100 cc, and on the following day it was 35 mg per 100 cc. The white-cell count was 22,000. Six days later it was 36,200. On the thirty-third hospital day he was transferred to this hospital.

Physical examination showed the patient to be oriented and in only slight distress. The skin was warm and moist. The tongue was red and heavily coated. There was some bleeding about the gums. There were dullness and many bubbling rales at the right base. The abdomen showed slight tenderness. Peristalsis was normal. On the right side of the abdomen there was a large wound dehiscence, with viable bowel lateral to the rectus muscle. Two

stomas, one of the ileum and another of the colon, were thought to be identified. There was extensive undermining into the flank, with draining sinuses. The rectum was filled with barium.

The temperature was 100°F, and the pulse 92. The blood pressure was 95 systolic, 70 diastolic.

A review of the symptoms revealed that the patient had been accustomed to drinking a half to two bottles of beer a day for many years and that during the present illness he had drunk up to a pint of whisky a day. He had had no previous operations or serious illnesses. He usually had two or three bowel movements daily.

Two days after admission laboratory study revealed a serum nonprotein nitrogen of 35 mg per 100 cc, and the total protein was 6.41 gm, the albumin 3.85 gm, and the globulin 2.56 gm per 100 cc (albumin-globulin ratio, 1.5). The serum chloride was 84, the sodium 119.6, and the potassium 5.6 milliequiv per liter. The cephalin flocculation test was negative in twenty-four hours and \pm in forty-eight hours. The van den Bergh reaction was normal. The white-cell count was 23,200, the blood hemoglobin was 10.7 gm. The urine was negative for albumin. The prothrombin time was 19 seconds (normal, 16 seconds).

Roentgenograms of the chest and abdomen taken on the second hospital day showed plate-like atelectasis at the left base and some fluid in the left pleural cavity. There was no distention of the large or small bowel. There were remains of barium in the transverse colon and rectum. There was no definite evidence of free air beneath the diaphragm.

In the hospital the patient's condition became progressively worse. The chest became full of rales, and respiration was difficult. On the fourth hospital day the temperature suddenly rose to 103°F, and the white-cell count to 36,400. The abdomen was somewhat distended, although there were large quantities of fecal drainage. The following day a Harris tube, which had been passed the day before in preparation for a proposed ileotransverse colostomy, was found coiled in the stomach and withdrawn. Nearly all the gas had disappeared, and there appeared to be less abdominal distention. The next day a barium enema showed no obstruction as far as the hepatic flexure. The cecum and ascending colon could not be outlined. Examination of the blood at that time revealed a sodium of 130.7, chloride of 91, potassium of 3.3 and carbon dioxide of 30.5 milliequiv per liter. The fasting blood sugar was 87 mg per 100 cc. The white-cell count was 18,500, with 77 per cent neutrophils.

On the seventh hospital day the patient developed symptoms suggestive of delirium tremens with "shakes" and hallucinations. He became semidelirious and was incontinent of urine. The pulmonary situation became critical, with progressive respiratory embarrassment. There were coarse

rales and rhonchi over the entire chest. Repeated catheter suctioning of the tracheobronchial tree was productive of a large amount of thick, stringy, whitish, tenacious mucus.

On the tenth hospital day the temperature had risen to 105°F. The total protein was 5.8 gm per 100 cc, the amylase 22 units per 100 cc, and the carbon dioxide 26.9 and the chloride 100 milliequiv per liter. The calcium was 7.8, and the phosphorus 3.4 mg per 100 cc. The urine output dropped to 750 cc, and the nonprotein nitrogen rose to 60 mg per 100 cc. The patient was flushed and mildly cyanotic. The blood pressure was unobtainable. The pulse rate was 150, and the respirations 44.

The following morning, on the twelfth hospital day, the temperature had risen to 106°F, shortly after which the patient died.

DIFFERENTIAL DIAGNOSIS

DR MARSHALL K. BARTLETT: May we see the x-ray films?

DR STANLEY M. WYMAN: The original films of the chest show the left leaf of the diaphragm elevated, and there is horizontal linear density, which appears to lie chiefly in the region of the left lower lobe. There is no definite or significant fluid made out in the pleural space in the lateral view, but there is a suggestion of some blunting of the costophrenic angle in the posteroanterior view. The same day an upright film of the abdomen shows a gas-filled stomach at a considerable distance from what I take to be the diaphragm, and there is some suggestion of mottled rarefaction adjacent to the undersurface of the diaphragm. This is not definite but suggests gas in the space below the left leaf of the diaphragm. A film taken four days later shows essentially the same process, with atelectasis of the left lower lobe and a little more suggestion of fluid in the left costophrenic sinus. A film taken still later, at the time of barium-enema examination, shows no definite intrinsic lesion in the colon, but it does show a coiled tube in the stomach. Again, there is a suggestion of mottled rarefaction adjacent to the left leaf of the diaphragm, possibly lying below it. The last film of the chest shows essentially a progressive change, with atelectasis and probably fluid.

DR BARTLETT: Let us approach this problem by going back to the first admission to the outside hospital and see what the history seemed to be then and, putting that together with the operative findings, see if we can figure out any condition that will fit this picture. In the first hospital admission there was a history, going back approximately two months, of dull, crampy, epigastric pain, lasting a few minutes, occurring several times a day and relieved by two or three glasses of whisky. Then we have the statement that for many months he had a desire to defecate without success. Later in the history we are told that the normal bowel move-

ments were two or three a day. This may have represented a change in bowel habit. He went along like that until about a week before admission, when the pain became more severe, and he began drinking more to relieve it, without success. At that time he had nausea and vomiting of gastric contents. That is the only time in the story that he had nausea and vomiting. On admission the striking thing in the physical examination seemed to be that the abdomen was distended, the upper portion more so than the lower portion. For the first three days in the hospital he had a temperature of 99°F and a normal pulse. The white-cell count was normal until after operation, and then it rose to more than 20,000. At operation a normal appendix was found. However, the large bowel was distended, and a note was made that "the intestine showed acute enteritis." It is not specified whether this was the large or the small bowel. I assume, since it is a separate statement, that it refers to the small bowel. Its color was purple. What condition could produce that picture? The changes in bowel habit and the facts that at operation the colon was distended and that on barium enema the barium did not pass the hepatic flexure certainly bring to mind the possibility of an obstructing lesion in the large bowel. On the other hand, there are a good many things that seem hard to explain with that diagnosis. The location of pain during the two months before admission was epigastric. Certainly, lesions of the colon usually produce pain at a lower level than that. We are all probably familiar with the experimental work that Dr. Chester M. Jones did some years ago by distending balloons at various levels of the gastrointestinal tract to see where pain was produced in the abdomen. Distention of the hepatic or splenic flexure might produce pain in the right or left upper quadrant, but this epigastric pain is hard to explain on the basis of a lesion in the colon. It is also hard on that basis to explain the fact that the distention was limited to the upper abdomen, and the colostomy does not seem to have done any good, so I do not believe that an obstructing lesion of the colon fits the picture very well.

What lesion of the small bowel could he have had? Could it have been a tumor? A lesion like that should express itself either by obstruction or by bleeding. We have no evidence here that he had massive bleeding into the gastrointestinal tract. Could he have had an obstructing lesion in the small bowel? I think it would be very unlikely to have such a sudden change in the picture, with his mild symptoms becoming quite suddenly worse, unless we assume that the lesion perforated, but if such were the case, the findings at laparotomy would have been different. If he had a small-bowel obstruction, we would not expect the colon to be dilated and we would expect that both dilated and collapsed loops of small bowel would be found. So I do not believe that fits the picture very well.

It is noted that the bowel was almost purple. That suggests interference with blood supply. Could it have been a mesenteric thrombosis? I think that is unusual with such a gradual onset. Mesenteric thrombosis should have been a more acute picture, and I doubt if the outcome would have been so long drawn out.

Could this have been regional enteritis? Of course, the thing that brings that to mind is the fact that he developed a spontaneous small-bowel fistula where the colostomy was done, and since regional enteritis is notorious for forming fistulas, we must consider it. So far as the history is concerned, any change in the bowel habit has been in the direction of constipation rather than toward diarrhea. I think the pain could be consistent with an inflammatory lesion in the small bowel, but I rather expect that the description of the findings would be different at operation in that event. As we all know, regional enteritis is typically a fairly circumscribed or localized lesion. There may be multiple areas, but usually they do not cover a great extent of bowel in any one area. However, it is a possibility. I do not see how we can rule it out. Again, the distention, if due to a small-bowel lesion, would probably have been generalized and not limited, as this was, to the upper abdomen. Perhaps I am putting too much stress on that finding, but certainly it is emphasized in the history.

To move up the gastrointestinal tract — could this have been gall-bladder disease? It would be very atypical, and I do not believe the evidence fits the picture particularly well. It would not account for the changes in the small bowel at operation. The distention of the colon, perhaps, could have been purely secondary — that is, paralytic. Could this have been pancreatitis? I do not see how one can rule it out. It is unusual for pancreatitis to cause mild symptoms for a period of two months and then an acute attack. I would like that possibility better if this had come on suddenly, out of a clear sky. Pancreatitis typically occurs after a large meal or the ingestion of a considerable amount of liquor. This man drank quite a lot, but the onset was not typical. The normal amylase taken a month after the onset of the attack does not rule pancreatitis out at all. Typically, the amylase goes up in the first twenty-four or forty-eight hours and then comes down to normal. It could have come down long before this determination was

made and still that diagnosis could be the correct one.

How about acute gastritis? I should think it could produce the symptoms that he had up to the day he came into the hospital, — mild, dull, crampy, epigastric pain, — but it is hard to explain the development of acute, severe pain on the basis of simple gastritis.

How about an ulcer of the stomach or duodenum or possibly a gastric neoplasm that had perforated? I believe the history of the symptoms for two months before entry fits that reasonably well. I think the increase in pain for a week before admission could be explained on the basis of gastritis, the sudden, severe pain the day before admission representing a perforation. If we assume that it was one of those rare situations in which the perforation was into the lesser peritoneal cavity, which then became distended with air and fluid, we perhaps can explain the difference between the upper and lower abdominal distention. Could that explain the operative findings? If we do assume that he had perforation in the upper abdomen, even in the lesser peritoneal cavity, there probably would have been some leakage of irritating fluid into the general peritoneal cavity, resulting in generalized peritonitis, which might have caused the changes noted in the bowel. Distention of the large bowel we would assume on the basis of paralytic ileus, and the fact that colostomy did not work reinforces that thought. Was this an ulcer or a neoplasm? I cannot see any way to be sure of either. The patient was forty-eight and had a short history. It seems on a chance that it is more likely that he had ulcer than neoplasm, with perforation.

Accepting the situation as it was at operation, what happened from there on? It seems to me that it is all relatively simple. A small-bowel fistula developed. Why it developed I cannot be sure. If he had regional enteritis, that is reason enough in itself, or it is possible that in closing the wound in a distended patient, some injury was done to the bowel, which in the course of several days could have resulted in perforation. He developed a small-bowel fistula, wound sepsis, a great deal of loss of fluid and electrolytes from the small-bowel fistula, resulting in the imbalance in the blood chemistry that is outlined. Also, there seems to have been very little question that he had a septic process in the left upper quadrant under the diaphragm. There

is certainly a strong suggestion in the x-ray picture

A barium enema was then done. If this patient had a lesion of the upper abdomen, why did the barium enema fail to fill the right colon? I cannot answer that. I do not know whether it is safe to rule out an organic lesion in the hepatic flexure. I am inclined to do so and to say that this was something high up in the abdomen. The course was steadily downhill—a losing struggle against sepsis and a small-bowel fistula. The downhill course continued with progressive pulmonary difficulties. There was a thought at one time that ileotransverse colostomy could be done. That was probably on the basis of a rather desperate attempt to correct the fluid and electrolyte loss from the small bowel by short-circuiting the fistula and the colostomy. The patient was apparently not well enough to allow that to be done and went rapidly downhill and died. It seems that the downhill course was a mixture of sepsis, fluid and electrolyte loss, and pulmonary difficulties, with probably terminal bronchopneumonia.

CLINICAL DIAGNOSES

Wound dehiscence, with small-bowel fistulas
Chronic alcoholism, with delirium tremens
Bronchopneumonia

DR BARTLETT'S DIAGNOSES

Gastric ulcer, with perforation
Small-bowel fistulas
Bronchopneumonia

ANATOMICAL DIAGNOSES

Acute pancreatitis, with perforation of transverse colon and abscess formation
Peritoneal abscesses, with fat necrosis
Small-bowel fistulas
Operation colostomy
Pulmonary atelectasis
Pulmonary edema
Hepatomegaly, with fatty vacuolization
Acute splenitis with splenomegaly

PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN At autopsy there was, as to be expected, a lot of sepsis around the

two colostomies that were present in the right lower abdomen. When the abdominal cavity was opened there was a gush of gas, the omentum was plastered down over the peritoneum and was thick and porky, suggesting long-standing sepsis. When that was elevated a relatively small pocket of pus in the right lower quadrant was broken into. It probably was secondary to three fistulas in that region. In lifting the transverse colon the examiner broke into a very large, greenish-black abscess, which involved the region of the hilus of the spleen and tail of the pancreas, and extended up under the left diaphragm, which corresponds to gas seen on the x-ray film. Surrounding this abscess and all over the omentum close by was a lot of chalky-white material characteristic of fat necrosis. Further dissection showed that the entire tail of the pancreas had become necrotic and that the pancreatic abscess had extended medially to involve the upper surface of the body and head of the pancreas. I should think that the entire process was probably due to a pancreatitis that perhaps started slowly and finally produced an overwhelming infection of the pancreas. The abscess had broken into the transverse colon, and that undoubtedly added to the sepsis and accounted for some of the gas that we saw on the film. There was no primary lesion in the stomach or any part of the colon. The small-bowel loops were matted together in the right lower quadrant, but only there. I do not understand the description, at the first operation in the other hospital, of the purplish bowel—unless some loop was strangulated at one time and then untwisted. We did not find anything like that, except the sepsis between the loops of bowel in the right lower quadrant.

DR BARTLETT Did you find any cause for the small-bowel fistula?

DR CASTLEMAN Nothing except the sepsis around the colostomy. He had a large, fatty liver (weighing 2700 gm), which might have been expected in a chronic alcoholic. The spleen was also enlarged (weighing 400 gm), but that may have been due, in part, to the sepsis. There was no fluid in either pleural cavity. Both lungs were pushed superiorly by the elevated diaphragm, and, in addition to the atelectasis, there was moderate pulmonary edema, but no foci of pneumonia.

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MEDICAL PREPAREDNESS

TEN years ago there was much talk of medical preparedness, along with other kinds of preparedness for war. Activity that began at that time under the banner of preparedness has been almost continuous and has often been carried on by the same individuals or committees, but the word on the banner changed, first to *defense*, then to *victory* and then to *post-war planning*. Planning for what? Why, for preparedness, of course. So now it is beginning all over again, the world changes, but not the emotions of mankind!

In a recent Washington Report on the Medical Sciences it is stated that the "Army medical department is industriously gathering information on

establishment and operation of its own medical school." The statement makes it clear that nothing beyond the possible release of a few trial balloons is contemplated for the immediate present, but the idea of an Army medical school, as a means to an end, is worthy of careful consideration. In its favor would be the fact that once established, it would at least provide a group of men who had committed themselves to a career in military medicine. Although the number of such men could never provide sufficient personnel for wartime needs, it might well supply a nucleus round which civilian physicians would gather in times of emergency. It might also lead to an eventual recognition of the importance of military medicine among medical educators as a whole. On the other hand the Army's present plan of assigning a medical officer to the faculty of existing medical schools on a co-operative basis might be developed to give quicker and larger results, and at a lower unit cost to the Government.

All medical schools are today in a difficult financial position. For even the richest of universities the establishment of a new medical school is a major undertaking. An Army medical school would not be embarrassed regarding finances, however, even were it organized on a lavish scale it would be a trivial item on the federal budget. An Army school would be more apt to encounter difficulties in mustering an outstanding staff of teachers, such organization takes time, and in the matter of preparedness time again is of the essence. Unless it can be clearly seen that advantages will quickly flow, the project should not be advised.

Assuming that an adequate staff could be mustered within a period of two years and that it could be completely protected from political and other pressures (a *sine qua non* for success), it would be 1955 before the first class would emerge into anything useful from a medical point of view. An alumni body could not aggregate into useful volume before 1960 at the earliest, and the accumulation of that intangible thing called tradition, without which no institution can attain its maximum effectiveness, would lie still farther in the future.

It may be that the need is sufficiently urgent to consider initiating an Army medical school—

not to meet the present call for preparedness, but to prepare for the next time preparation may be called for. If there is reason to believe that the demand for military doctors is a long-range one that must be built into the national economy from this time forward, action should be taken. One cannot help feeling that the Army's medical record is a proud one as it stands, from Shippen to Bliss. Under these men and those who have served between them the Army has produced its Warrens, its Beaumonts and its Reeds. Could it have done so if it had been just another medical school? As one looks back over history one cannot help observing that the Medical Department of the Army has been conspicuously successful in extracting the best available talent from the profession as a whole when it was needed and in as sufficient volume as can ever be permitted by the exigencies of war.

TEACHING IN VETERANS ADMINISTRATION HOSPITALS

THE report on the practice and teaching of surgery in Veterans Administration hospitals, which appears elsewhere in this issue of the *Journal*, deserves careful reading and thoughtful consideration. There are several aspects of this matter that are closely tied with the socioeconomic problems of medicine today.

The execution of the plans formulated under General Hawley's tenure of office was, in large measure, the result of far-seeing policies envisioned by the late Dr. Elliott C. Cutler. The first and foremost goal was, and still is, the optimum care for the veterans in the Veterans Administration hospitals. That this primary purpose has, to a very gratifying extent, been accomplished is apparent from the report, and is clear and unmistakable to those who are associated with these "affiliated hospitals." To accomplish this, the most important step was to bring the hospitals in close connection with, and under the supervision of, the dean's committee of the various medical schools with which these hospitals are now affiliated; these dean's committees have, practically speaking, complete control of the appointment of the professional staff that serves the hospitals. The consultants, the attend-

ing surgeons and the resident staff must all be approved by the dean's committee before their names are sent to the administrative side for formal appointment. Thus, it has been possible to obtain a staff of well trained men of recognized surgical ability and with experience and interest in teaching. The selection of these men is now practically free from any political influence, however well intentioned that might be. The positions are given for professional merit alone. To quote the article: "In a word, they bring the medical school to the hospital." The senior consultants are men of known reputation as surgeons and teachers. The attending surgeons are younger, but, being free from administrative responsibilities, they do the bulk of the daily bedside and operating-room instruction. They handle the more difficult cases themselves, but, in general, their function in the operating room is to supervise and to assist personally the resident staff. To quote further, "It may be well to emphasize that the attending surgeon cannot be a man of limited experience hoping to broaden himself by operating in the Veterans Administration hospitals. He must be an accomplished surgeon, capable and willing to teach. His role is a comparatively selfless one." The presence of a well trained resident staff is a great asset to any hospital. Its advantages are obvious, and as the author of the article points out, the comparison between the hospital with the medical-school affiliation and that without one is most striking. That the care received by the patients in the affiliated hospitals is better admits of no argument. By proper utilization of the affiliated hospitals as teaching centers, great benefit comes to the patient. This policy has also provided a larger field for the proper training of the young surgeon. Both parties have benefited greatly.

What of the future? As long as the present policy continues, the patient in the Veterans Administration hospital will continue to receive a very high quality of care — as he should. But, as the author points out, such a system cannot be expanded too far without becoming administratively top-heavy, with disastrous results. "The machine would control the men, and the control of the patient would be in the grip of an automaton." But whatever

changes that lie ahead of us in the future, the medical profession cannot allow, through inertia or lack of interest, the actual professional care of patients in Veterans Administration hospitals drop to the low levels that were once the rule

THE MERRY WIDOW

GREER reports on another page in this issue of the *Journal* his experiences with victims of the double-barbed widow whose kiss is sometimes death. They are of more than passing interest, for this antiscindal vagrant, her egg sac flung over her back, her symbolic hourglass, its sands of time forever running out, stamped upon her ventral aspect, is readily widening her range even into those austere regions of New England north of Boston. *Latrodectus mactans*, despite her reputation, is neither sadistically merry nor brutally aggressive. Instead she is apparently a shy, timid and confused creature who kills her mate at the call of instinct rather than from sheer wantonness. She is more to be pitied than censured, for she seems doomed never to know the tranquil joys of domesticity. In view of the extreme toxicity of the venom with which she is armed, however, it is comforting to know that she attacks only when cornered, and to learn the effectiveness of calcium gluconate as an antidote for her bite.

NOTES FROM THE MEDICAL EXAMINER

IN THIS issue of the *Journal* a new department is initiated under the title "Notes from the Medical Examiner." It is the hope of the editors that this department, appearing at approximately monthly intervals, will meet with the approval of its readers and may be continued as long as it proves to be of value.

"Notes from the Medical Examiner" will be a department devoted to ground common to the specialist in legal medicine and to the clinician, whether specialist or general practitioner. It will include such matters as procedures and technical methods evolved from the study of cases terminating in the jurisdiction of the medical examiner's office, discussions of groups of cases ending fatally as a result of unpredictable deficiencies or hazards

in treatment or diagnosis, discussions of the legal and medical aspects of obscure and sudden deaths, and reviews of legal medical subjects, including toxicology, pathology and clinical subjects that are now dispersed in a variety of medical and other technical journals.

MASSACHUSETTS MEDICAL SOCIETY

VETERANS IN FOREIGN MEDICAL SCHOOLS

At the meeting of the Council held on October 6 a resolution (as printed in the December 2 issue of the *Journal*) disapproving a policy of the Veterans Administration advising veterans that they may attend foreign medical schools at the expense of the Government was unanimously adopted by the Council.

Copies of the resolution were sent to every Massachusetts senator and congressman. Each has received the following letter from the Veterans Administration concerning the problem:

Honorable Richard B. Wigglesworth
United States Representative
Milton, Massachusetts

Dear Mr. Wigglesworth:

This will acknowledge receipt of your letter of October 30, 1948 with which you enclosed a copy of a resolution adopted by the Council of the Massachusetts Medical Society relative to the approval by the Veterans Administration of medical schools located in foreign countries to provide training to American veterans of World War II, under the provisions of Public Law 346, 78th Congress, as amended.

The resolution has been read carefully and the contents thereof noted with interest. The statement contained in the resolution that "the Veterans Administration in Washington is advising veterans that they may attend any medical school in Europe at the expense of the Government, and . . ." is not consistent with the facts.

A copy of the *New England Journal of Medicine* was forwarded to the Veterans Administration by Dr. George C. Shattuck under date of July 29, 1948. Special attention was invited at that time to the editorial "Of Thee I Sing" and the reprint of a letter addressed to the editor by Dr. A. H. A. Campbell, 520 Commonwealth Avenue, Boston 15, Massachusetts, relative to the article by Dr. J. L. Lochner, Jr., Secretary of the Board of Registration for the State of New York, which appeared in the May 1, 1948, issue of the *Journal of the American Medical Association* entitled, "Licensure Evaluation of European Medical Graduates."

Dr. Shattuck was advised under date of August 24, 1948 that Public Law 346, 78th Congress as amended, provides in part that, "Such person (an eligible veteran) shall be eligible for and entitled to such course of education or training, full time or the equivalent thereof in part-time training, as he may elect, and at any approved educational or training institution at which he chooses to enroll, whether or not located in the State in which he resides, which will accept or retain him as a student

or trainee in any field or branch of knowledge which such institution finds him qualified to undertake or pursue."
(Parenthetical statement added)

It was further emphasized in this connection that the Veterans Administration approved educational institutions to provide training under the above legislation. It does not accredit institutions, evaluate credits, or pass on the standards of one institution as compared with another. Every effort is made to approve only those institutions which are found to be qualified in accordance with the criteria established for approving educational institutions by the Veterans Administration. These criteria cover such factors as control, staff, plant and equipment, curriculum, finances, stability etc. Only in very exceptional cases are foreign educational institutions now approved which have been established subsequent to 1939.

With regard to the statement contained in the resolution that the Veterans Administration is advising veterans that they may attend any medical school in Europe, your constituents may be advised that it is the policy of the Veterans Administration to inform all veterans making inquiry concerning the possibility of pursuing medical training outside of the United States that most of the state boards of medical examiners, as well as the American Medical Association, have definite restrictions on recognition of work done in schools of medicine in foreign countries. They are informed that in more than a third of the states graduates of medical schools outside of the United States and Canada are not eligible for licensure. They are furnished with the list of eighteen states in which credentials from medical schools in foreign countries are not accepted, as shown in the *Journal of the American Medical Association*, May 13, 1945. Each inquiring veteran is informed that if he is planning to practice medicine in the United States, it is strongly advised that he check with the state board of medical examiners in the state in which he expects to practice, as to the acceptability of work from the foreign medical school which he has under consideration.

The Veterans Administration has had considerable correspondence with the Secretary of the American Medical Association relative to the matter of approval of foreign medical schools to provide training under Public Law 346. The Secretary recently furnished this office with several copies of a reprint from the *Journal of the American Medical Association*, May 17, 1947, Vol. 134, P. 278, "Requirements for Candidates for Medical Licensure on the Basis of Credentials Obtained in Countries Other Than the United States and Canada," and several copies of a directory of "Medical Examining and Licensing Boards" in the United States. Copies of this material have been furnished to each of the five offices of Attaches for Veterans Affairs located at the American Embassies, London, England, Paris, France, Rome, Italy, Mexico City, Mexico, and the American Consulate, Geneva, Switzerland. The Office of Attache for Veterans Affairs at London, has jurisdiction over Vocational Rehabilitation and Education matters in the United Kingdom, Eire, Norway, Sweden, and Denmark, the Attache at Paris has jurisdiction over France and Belgium, while the other Attaches have jurisdiction over such matters in the countries where they are located.

It may be of interest to your constituents to know that as of April 30, 1948, there were only 261 United States Veterans pursuing courses in the various fields of medicine in foreign countries under Public Law 346. Many of these veterans were pursuing postgraduate study in various specialized fields, having already obtained M.D. degrees. Fifty-five of the 261 were enrolled in approved schools in Canada. Forty-two of the number were pursuing training in England and Scotland. Four were enrolled in Ireland.

In conclusion it may be emphasized that it is not necessary for a veteran to inform the Veterans Administration that he intends to practice his profession in the United States or in a foreign country. In every instance where inquiry has been made of this office, the veteran has been alerted to the potential difficulties he must expect in securing license to practice in the United States. Therefore, in securing a medical education in a foreign country, veterans who consult us first do so of their own volition, and with full knowledge of the obstacles which

may make it impossible to practice their chosen profession in this country.

Please be assured that your interest in the welfare of veterans is very much appreciated.

O W CLARK

Executive Assistant Administrator

Veterans Administration

Under Public Law 346 the Veterans Administration, by implication, is constituted the approving authority for schools of all types. Since the Veterans Administration, according to Mr. Clark's letter, has consulted the American Medical Association "relative to" foreign medical schools, it is to be hoped that the approval of that organization, which is the acknowledged authority on medical schools, will be made a *sine qua non* of recognition of any medical institution by the Veterans Administration.

If Public Law 346 contains no criterion of minimal professional standards for courses in which veterans participate and if there is no stipulation regarding the value to the veteran of the knowledge and skill acquired, the law should be amended. It is questionable whether veterans should be permitted to take courses, at the taxpayers' expense, that will be worthless. When such a course is "chicken sexing," as pointed out in the editorial "Of Thee Sing," a waste of public money is all that is at stake but when study in unapproved medical schools is involved, the threat to acceptable medical standard in the United States is a matter of the gravest concern to physicians.

H QUIMBY GALLUPE, *Secretary*

NOTES FROM THE MEDICAL EXAMINER

THE TOXICOLOGY OF ALCOHOL

No chemical known to man is responsible for so many deaths, lost manpower days and traumatic injuries as ethyl alcohol. It is directly or indirectly responsible for more than 50 per cent of all deaths caused by chemical agents.¹

Metabolism

Ethyl alcohol is completely absorbed from the gastrointestinal tract within one to three hours of ingestion. Its concentration after complete absorption is proportional to the water content of the individual tissue. Thus, the blood level provides a reliable index of that in brain tissue at all times in the postabsorptive period. The disappearance of alcohol from the body results from both oxidation and excretion (about 95 per cent by the former). Regardless of the dose, alcohol does not remain in the living body longer than twenty-four hours.

The oxidation probably does not exceed 5 to 10 gm an hour or from 0.02-0.04 per cent an hour. The toxicity is purely that of an acute central-nervous-system depressant. A late manifestation of alcohol intoxication is a shift of water from an

intracellular to an extracellular situation,² a possible explanation for the thirst occurring during and after the alcoholic debauch

Alcohol as a Cause of Death

Alcohol may cause death either by acute narcosis or by initiating or accentuating physical and mental abnormalities in the patient and thus predisposing him to a variety of fatal misadventures³

Deaths due directly to alcoholism Ethyl alcohol is an anesthetic agent and in sufficient amounts kills by medullary paralysis. When death occurs relatively early in the postabsorptive phase (not the usual time for death) the blood alcohol concentration may be as high as 0.5 per cent or even higher. Frequently, death does not occur until several hours or longer after the onset of coma. Owing to continued metabolism, the post-mortem blood alcohol concentration may be well below 0.5 per cent. Alcoholic addicts frequently, by accident or design, take large doses of a barbiturate compound. There is an additive depressant action by these two anesthetic drugs.⁴ Complications of the alcoholic coma may be responsible for death, such as acute asphyxiation by food aspirated into the air passages or hemorrhagic pulmonary edema from the inhalation of liquid gastric juice. A series of alcoholic debauches may render the patient more susceptible to infection, particularly of a respiratory nature.

Hepatotoxic chemicals such as the halogenated hydrocarbons may be accentuated by acute and chronic alcoholism. The evidence to date does not specifically incriminate alcohol in the pathogenesis of liver cirrhosis except upon the basis of nutritional deficiency.⁵ Acute and chronic pancreatitis is said to be more common among alcoholic addicts,⁶ but this has not been our experience. The pathological nervous-system change in chronic alcoholism is obscure except in relation to deficiency diseases—for example, Wernicke's disease⁷ and polyneuritis. Fatal circulatory collapse may develop unpredictably and uncontrollably in acute delirium tremens related perhaps to the severe physical overexertion. In several cases severe hyperthermia of undetermined cause has been observed as a terminal event.

Deaths due indirectly to acute alcoholism Predisposition to misadventure accounts for more deaths than the direct pharmacologic effect. Fully 50 per cent of drivers and nearly one third of pedestrians involved in fatal accidents are termed to have been "under the influence."⁹ It is not unusual for the inebriate to commit suicide—an act that he would probably not have consummated in his alcohol-free moments. About 50 per cent of persons homicidally slain had been drinking, according to the case records of the Department of Legal Medicine of Harvard Medical School. Obviously, it may be of great legal importance to know whether the perpetrator or victim of violence

was under the influence of alcohol and the degree of that influence.

Levels of Intoxication in Relation to Blood Alcohol Concentration

Most people show definite and obvious signs of intoxication at 0.25 per cent, a level requiring in the average adult the ingestion of approximately 12 ounces of whisky or the equivalent within a few hours. Although many persons show evidence of intoxication at lower blood levels, few, if any, fail to have obvious impairment of physical and mental faculties at concentrations higher than 0.25 per cent. High dilution of the alcohol beverage or food in the stomach may unpredictably lower the absorption rate. Those accustomed to drinking often show less severe outward manifestations of ingestion than the occasional drinker or the neophyte. Coma approximating surgical anesthesia is reached usually at levels of 0.4 per cent or above.

The National Safety Council has adopted the concentration 0.15 per cent alcohol in the blood as *prima facie* evidence of intoxication with respect to the operation of a motor vehicle. At this concentration not all people (perhaps 50 per cent) show significant behavior alterations on casual examination. In Evanston, Illinois, drivers with more than 0.15 per cent alcohol in the blood were fifty-five times more likely to become involved in a personal-injury accident than drivers with no alcohol.⁹

Specificity

With practically all present-day methods, alcohol is determined indirectly by estimation of the volatile reducing material of the specimen by distillation or by desiccation.¹⁰ In the presence of putrefaction, analysis is unreliable because of the formation of incompletely identified volatile reducing substances. Since liver tissue oxidizes alcohol after death, it should not be used.

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WALTER W JETTER, M D
Assistant Professor of Legal Medicine
Harvard Medical School

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Executive Assistant Administrator
Veterans Administration

Under Public Law 346 the Veterans Administration, by implication, is constituted the approving authority for schools of all types. Since the Veterans Administration, according to Mr. Clark's letter, has consulted the American Medical Association "relative to" foreign medical schools, it is to be hoped that the approval of that organization, which is the acknowledged authority on medical schools, will be made a *sine qua non* of recognition of any medical institution by the Veterans Administration.

If Public Law 346 contains no criterion of minimal professional standards for courses in which veterans participate and if there is no stipulation regarding the value to the veteran of the knowledge and skill acquired, the law should be amended. It is questionable whether veterans should be permitted to take courses, at the taxpayers' expense, that will be worthless. When such a course is "chicken sexing," as pointed out in the editorial "Of Thee I Sing," a waste of public money is all that is at stake, but when study in unapproved medical schools is involved, the threat to acceptable medical standards in the United States is a matter of the gravest concern to physicians.

H. QUIMBY GALLUPE, Secretary

NOTES FROM THE MEDICAL EXAMINER THE TOXICOLOGY OF ALCOHOL

No chemical known to man is responsible for so many deaths, lost manpower days and traumatic injuries as ethyl alcohol. It is directly or indirectly responsible for more than 50 per cent of all deaths caused by chemical agents.¹

Metabolism

Ethyl alcohol is completely absorbed from the gastrointestinal tract within one to three hours of ingestion. Its concentration after complete absorption is proportional to the water content of the individual tissue. Thus, the blood level provides a reliable index of that in brain tissue at all times in the postabsorptive period. The disappearance of alcohol from the body results from both oxidation and excretion (about 95 per cent by the former). Regardless of the dose, alcohol does not remain in the living body longer than twenty-four hours.

The oxidation probably does not exceed 5 to 10 gm an hour or from 0.02-0.04 per cent an hour. The toxicity is purely that of an acute central-nervous-system depressant. A late manifestation of alcohol intoxication is a shift of water from an

be demonstrated in the sputum. All this and much more has come to be known as associated with the personality of the author.

The reviewer hoped that in this new book he would find some of the newer aspects of pathology, diagnosis and treatment that belong to the 1948 era. He looked for longer discussion of tuberculous bronchitis, its implications regarding the dynamics of cavities or the effect of bronchial stenosis on the clinical course of the disease.

The author devotes considerable space to outdoor and light treatment as well as tuberculin therapy, but gives very little detailed discussion on the indications and mode of treatment with streptomycin.

The term "compression therapy" hardly has a place in a modern book on tuberculosis, and yet it is quite loosely used together with "collapse therapy." The two are certainly not synonymous any more than two other terms — phrenicectomy and phrenicotomy — that are used indiscriminately.

Since lobectomy and pneumonectomy have a place in the general scheme of tuberculous therapy and since this type of treatment requires the greatest experience and clinical judgment, the reader has a right to expect much more guidance on this subject than the few paragraphs allotted to it in this book.

Certainly, the author is still the great scholar and the great interpreter of phthisiogenesis with its multifiform pathologic lesions and the effect it has on the clinical course of the disease. His description of the neurologic manifestations of pulmonary tuberculosis is a gem and a classic.

Knowing therefore the erudition and the long experience of the author one expects an authoritative as well as an up-to-date treatise of the subject. Instead, this book is merely another edition of his old books.

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The general aims of this study were fourfold: to gather information on present-day teaching of the social and environmental aspects of medicine in the United States and Canada, to analyze the data obtained, to evaluate the methods and techniques of instruction in use, and to offer recommendations based on conclusions drawn from the study.

The Committee considers its report as an initial probing of the subject and recommends further study along special lines by professional organizations and other interested groups, and the individual medical study and evaluation of methods and techniques in this phase of teaching. The

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR NOVEMBER, 1948

DISEASE	RÉSUMÉ		
	NOVEMBER 1948	NOVEMBER 1947	SEVEN YEAR MEDIAN
Chancroid	5	3	2*
Chicken pox	1740	753	969
Diphtheria	37	18	18
Dog bite	806	620	620
Dysentery bacillary	3	21	22
German measles	59	60	60
Gonorrhea	262	234	378
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	1	0	0*
Malaria	1	5	15
Measles	2789	153	657
Meningitis meningococcal	3	4	12
Meningitis Pfeiffer bacillus	4	3	5
Meningitis pneumococcal	4	3	4†
Meningitis staphylococcal	0	0	0†
Meningitis streptococcal	0	1	0†
Meningitis other forms	1	0	0†
Meningitis undetermined	2	7	4†
Mumps	1020	461	523
Pneumonia lobar	62	48	162
Polio myelitis	3	15	24
Salmonellosis	3	8	7
Scarlet fever	467	304	704
Syphilis	183	235	391
Tuberculosis pulmonary	340	204	217
Tuberculosis other forms	19	10	12
Typhoid fever	1	1	2
Undulant fever	2	3	4
Whooping cough	253	647	647
* Four year median			
† Six year median			

COMMENT

Those diseases above the seven-year median are chicken pox, diphtheria, measles, mumps and tuberculosis all forms.

Those diseases with incidence below the seven-year median are bacillary dysentery, poliomyelitis, salmonellosis, scarlet fever, typhoid fever, undulant fever and whooping cough.

Chicken pox for the second month in succession is highest since beginning of reporting in 1916.

For the eighth month, mumps has the highest incidence since it was made reportable in 1916.

Diphtheria has the highest incidence since 1934, and measles the highest since 1925.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Anthrax was reported from Saugus, 1, total, 1.

Diphtheria was reported from Abington, 1; Arlington, 2; Boston, 18; Brockton, 1; Chelsea, 1; Dartmouth, 1; Framingham, 1; Gardner, 1; Lowell, 1; North Attleboro, 1; North Reading, 1; Somerville, 1; Waltham, 3; Winchester, 3; Winthrop, 1, total, 37.

Dysentery, bacillary, was reported from Lowell, 2; Medford, 1, total, 3.

Encephalitis, infectious, was reported from Millbury, 1; Pittsfield, 2; Worcester, 2, total, 5.

Lymphocytic choriomeningitis was reported from Barnstable, 1, total, 1.

Malaria was reported from Wellesley, 1, total, 1.

Meningitis, meningococcal, was reported from Boston, 1; Needham, 1; Spencer, 1, total, 3.

Meningitis, Pfeiffer-bacillus, was reported from Chicopee, 1; Lynn, 1; Pittsfield, 1; Saugus, 1, total, 4.

Meningitis, pneumococcal, was reported from Boston, 1; Northbridge, 1; Springfield, 2, total, 4.

Meningitis, other forms, was reported from Boston, 1, total, 1.

Meningitis, undetermined, was reported from Auburn, 1; Springfield, 1, total, 2.

Poliomyelitis was reported from Peabody, 1; Springfield, 1; Stoneham, 1; Worcester, 2, total, 5.

Salmonellosis was reported from Brookline, 1; Medford, 1; Wakefield, 1, total, 3.

Septic sore throat was reported from Boston, 6; Fall River, 1; Merrimac, 1, total, 8.

Trachoma was reported from Worcester, 1, total, 1.

Trichinosis was reported from Everett, 1; Fall River, 1; Gloucester 1; Hingham, 1, total, 4.

Typhoid fever was reported from Quincy, 1, total, 1.

Undulant fever was reported from Dartmouth, 1; Plymouth, 1, total, 2.

MISCELLANY

SEED FOR EUROPE

Two CARE seed packages containing potential harvest of food for human beings and fodder for livestock in Europe are now available for shipment.

Thirty-one selected varieties of vegetable seeds, enough to plant a garden up to 50 by 150 feet, are contained in the package designed for family use. The other, weighing 70 pounds, holds enough hybrid field corn seed to plant $2\frac{1}{2}$ acres and provide valuable feed for fattening meat animals or maintaining a high level of production in dairy cattle.

The new CARE packages are being offered for \$4 each, and orders are now being received by CARE at 50 Broad Street, New York 4, New York, as well as at all CARE offices throughout the country, for guaranteed delivery in eleven European countries. Orders should be sent at the earliest possible date to ensure delivery in time for the planting seasons.

The new packages may be ordered for delivery in Austria, Belgium, Czechoslovakia, Finland, Italy, France, Greece, the Netherlands, Poland, Great Britain (England, Scotland, Wales and Northern Ireland) and the American, British and French zones of Germany and Berlin.

CORRESPONDENCE

PROPER USE OF HOSPITALS

To the Editor: I should like to invite attention to the editorial in the *Norfolk Medical News* for November, 1948 especially the following quotation:

Numerous surveys have shown

6 Failure of hospital management to limit admissions to patients requiring hospital treatment

7 Failure of physicians to cease hospitalizing patients who might adequately be cared for at home

8 Tendency of physicians to continue employment of unnecessary laboratory procedures and expensive treatments

A concerted effort by both management and physicians will show effective result.

I have for some time been convinced that the major effort in the solution of this is right in the lap of the doctors of the hospital staff. If they fail to take the initiative before some body else does, they will have missed a major opportunity. It seems to me that finding No. 8 presents the chief challenge. Teaching hospitals have more reason perhaps to continue present practice, but a very desirable and far reaching reform could be initiated by making students, interns and residents (and the visiting staff too) conscious that some body has to pay the costs and that this is one of the items of medical expense about which something can be done.

Is there anything in medical socioeconomics that is more important?

ELMER S. BAGVALL, M.D., Chairman

Committee on Medical Economics
Massachusetts Medical Society

BOOK REVIEWS

Tuberculosis: A discussion of pathogenesis, immunology, pathologic physiology, diagnosis, and treatment. By Francis M. Pottenger, M.A., M.D., LL.D. 8° cloth, 597 pp., with 103 illustrations. St. Louis: The C.V. Mosby Company, 1948. \$12.00.

Those who have been brought up in the field of tuberculosis have come to know what to expect from the writings of the senior Dr. Pottenger. For nearly fifty years he has been an advocate of tuberculin therapy in pulmonary tuberculosis. He has written extensively on the importance of a very meticulous physical examination, extolling especially the fine points of inspection and palpation in the diagnosis of pulmonary tuberculosis. In fact, he claims to be able to diagnose pulmonary tuberculosis by palpation long before there is activity in the lungs and before tubercle bacilli can

be demonstrated in the sputum. All this and much more has come to be known as associated with the personality of the author.

The reviewer hoped that in this new book he would find some of the newer aspects of pathology, diagnosis and treatment that belong to the 1948 era. He looked for longer discussion of tuberculous bronchitis, its implications regarding the dynamics of cavities or the effect of bronchial stenosis on the clinical course of the disease.

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Committee is convinced that medical social teaching is undergoing rapid change and growth. The report is recommended for all medical libraries, medical schools and interested persons.

Control of Pain with Saddle Block and Higher Spinal Anesthesia. Edited by J. H. Walton, M.D. 8°, paper, 52 pp., with 5 illustrations and 12 plates. Summit, New Jersey: Ciba Pharmaceutical Products, Incorporated, 1948.

This short monograph presents the technics of spinal anesthesia in obstetrics and surgery, including abdominal section, with an additional chapter on nupercaine. The color plates are well done and effectively illustrate the text. The small volume should prove interesting to obstetricians and surgeons.

Children's Eye Nursing. By James H. Doggart, M.A., M.D. (Cantab.), F.R.C.S., Eng., ophthalmic surgeon, Hospital for Sick Children, Great Ormond Street, London, surgeon, Moorfields Eye Hospital, ophthalmic surgeon, St. George's Hospital, and lecturer in ophthalmology at St. George's Hospital Medical School. 12°, cloth, 144 pp., with 93 illustrations and 4 color plates. London: Henry Kimpton, 1948. 9/6 net.

This manual has been written for nurses. The material is well organized, and the text well written. The publishing is excellent. The manual should prove useful to all nurses.

Nature of Life. A study on muscle. By A. Szent-Györgyi, Department of Biochemistry, University, Budapest. 8°, cloth, 91 pp., with 22 illustrations and 7 plates. New York: Academic Press, Incorporated, 1948. \$3.00.

This small volume contains a series of lectures delivered by Dr. Szent-Györgyi at the University of Birmingham and the Massachusetts Institute of Technology. The lectures summarize the work done in the author's laboratory and discuss the histologic, molecular and electronic structure of muscle myosin and actin, actomyosin and the muscle fiber.

The Clinical Picture of Thyrotoxicosis. By Peter McEwan, M.A., M.B., Ch.B., F.R.C.S. (Edin). 8°, cloth, 127 pp., with 4 plates and 5 tables. Edinburgh: Oliver and Boyd, 1948. 15s net.

This monograph on toxic goiter has been written principally for the general practitioner, and emphasis has been placed on the clinical aspects of the disease. Thirty-one case histories have been interpolated throughout the text. The plate work is good, and the publishing is excellent. The small volume should prove interesting to physicians interested in the subject. It is pleasing to witness the return of high-class publishing in Great Britain.

Progress in Neurology and Psychiatry. An annual review. Volume III. Edited by E. A. Spiegel, M.D., professor and head, Department of Experimental Neurology, Temple University School of Medicine, Philadelphia. 8°, cloth, 661 pp. New York: Grune and Stratton, 1948. \$10.00.

In this third volume of a standard annual, over 2800 papers have been revised. Chapters have been added on mental deficiency and criminal psychiatry. Bibliographies are appended to the various chapters. The printing and type are excellent. A lighter paper could have been used to advantage. The series is recommended for all medical libraries and as a reference work to neurologists and psychiatrists.

NOTICES

ANNOUNCEMENTS

Dr. Raymond Gelfman announces the removal of his office to 83 Maple Street, Springfield.

Dr. James A. Halsted announces that his office is now at the Faulkner Hospital, Jamaica Plain, Boston.

Dr. Paul Graves Myerson announces the removal of his office to 1093 Beacon Street, Brookline.

GEORGE F. BAKER CLINIC

The Committee on Diabetes, appointed by action of the Massachusetts Medical Society, has suggested that clinical exercises in diabetes be offered without charge in various hospitals for physicians. To this end the George F. Baker Clinic at the New England Deaconess Hospital offers exercises on Monday and Friday of each week. The schedules are as follows:

Monday, 8:00-9:00 a.m., Second Floor, New England Deaconess Hospital. Case Presentations in Diabetes and Surgery of the Extremities.

Friday, 8:00-8:15 a.m. Second Floor, New England Deaconess Hospital. X-Ray Pathology in Diabetes. 8:15-9:00 a.m. Classroom, George F. Baker Building. Case Problems in Treatment of Diabetes and Complications. Pregnancies, acidosis, insulin resistance and so forth.

9:00-10:30 a.m. Medical Rounds for Visiting Physicians.

9:00-10:30 a.m. Instruction in Diet and Urine Testing (for Office Nurses, Technicians or Secretaries Sent by Physicians).

10:30-11:15 a.m. Class Teaching in Diabetes (Physicians, Office Assistants and Nurses are welcome).

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater of Building D, Harvard Medical School, on Tuesday, January 11 at 8:00 p.m. The chairman for the evening is Dr. Raymond D. Adams.

PROGRAM

The Correlation between Morphologic and Functional Disorders in the Motor-Nerve Cells in Poliomyelitis. Derek E. Denny-Brown and Joseph M. Foley.

An Encephalomyelitic Virus of Mice Causing Demyelinating Lesions of the Central Nervous System. F. Sargent Cheever, O. T. Bailey and A. M. Pappenheimer.

Pathological Changes in Carbon Monoxide Poisoning. Charles S. Kubik.

Subsequent meetings will be held on February 8, March 8, April 12 and May 10.

MEDICAL SOCIETY OF THE STATE OF NEW YORK

The annual meeting of the Medical Society of the State of New York will be held at the Hotel Statler, Buffalo, from May 2 to 5, inclusive.

(Notices concluded on page xix)

The *Journal* lacks extra copies of the July 29 and August 5, 1948, issues. If any subscribers who do not bind their copies have the above-mentioned issues on hand, the *Journal* will gladly pay 15 cents for each copy left at or mailed to its office (8 Fenway, Boston 15).

The New England Journal of Medicine

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Volume 240

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Number 2

A CLINICAL AND EXPERIMENTAL STUDY OF ISUPREL IN SPONTANEOUS AND INDUCED ASTHMA

FRANCIS C. LOWELL, M.D.,* JOHN J. CURRY, M.D.,† AND IRVING W. SCHILLER, M.D.‡

BOSTON

ONE of the synthetic analogues of epinephrine — 1-(3, 4-dihydroxyphenyl)-2-isopropylaminoethanol — has been studied under the name of aleudrin for a number of years in Europe. The experimental and clinical use of this drug in bronchial asthma and emphysema has been reviewed by Dautrebande,¹ and a report has been published in this country by Charlier.² The drug, administered as an aerosol, has been described as being especially effective in relieving attacks of bronchial asthma and significantly more active than epinephrine.

In this country Segal³ has reported excellent results in the treatment of bronchial asthma with the same preparation, also called isuprel, and Siegmund et al.⁴ found this drug to be the most active of a number of structurally related compounds in a study in guinea pigs using histamine and horse serum.

We have had occasion to observe the efficacy of isuprel in asthmatic patients in the outpatient clinic, among private patients on the hospital wards and also in association with experimental studies involving the induction of asthma-like attacks with histamine, acetyl-beta-methyl choline (methacholine) and certain allergenic extracts.

MATERIALS AND METHODS

Methacholine was injected intramuscularly in a concentration of 10 mg per cubic centimeter, and histamine acid phosphate was injected intravenously in a concentration of 0.2 mg per cubic centimeter. Allergenic extracts were prepared in phosphate buffer at a reaction of pH 7.4 containing 0.5 per cent phenol in a concentration of 1.20 by weight of dry pollen.

Isuprel§ was made available to us as a solution for administration by aerosol in a concentration of 1 and 0.5 per cent, in a concentration of 0.02 and 0.01 per cent for injection, and in tablets containing 10 mg for sublingual administration. The effectiveness of these preparations in relieving the signs and symptoms in asthmatic subjects was studied by the following methods.

Asthmatic subjects using this agent were observed for relief of asthma on the hospital wards or at home. The effectiveness of treatment was judged chiefly by statements made by the patients and to a lesser extent by changes in physical signs. The use of other preparations was not specifically discouraged, and there were frequent cases in which the efficacy of isuprel could be compared with that of other agents with which the patient was familiar.

Subjects with asthma were observed in the laboratory during spontaneous attacks, and changes in vital capacity and physical signs, as well as the degree of subjective relief, were observed after the administration of isuprel.

Similar observations were made in asthma-like attacks induced by exposure to aerosolized allergenic extracts, histamine and methacholine and by injections of histamine and methacholine according to technics that have been described elsewhere.^{5, 6}

The vaponephrin nebulizer or the No. 40 DeVilbiss nebulizer was used with a hand bulb by patients treating their asthmatic attacks outside the hospital, and these nebulizers supplied with pressure from an oxygen tank with the flow meter adjusted to read 6 to 8 liters per minute were also used on the ward and in the laboratory. Although the No. 40 DeVilbiss nebulizer may be somewhat less efficient than the vaponephrin nebulizer,⁷ we observed no difference between the two types in our studies.

*Associate professor of medicine, Boston University School of Medicine; member Robert Dawson Evans Memorial and director Allergy Clinic, Massachusetts Memorial Hospitals.

†Associate professor of medicine, Georgetown University School of Medicine; physician-in-charge, Diagnostic Service and visiting physician, Georgetown University Hospital; formerly assistant professor of medicine, Boston University School of Medicine; assistant member, Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals.

‡Instructor in medicine, Boston University School of Medicine; member Allergy Clinic, Massachusetts Memorial Hospitals.

§Handily supplied by Winthrop-Stearns Incorporated, Boston.

During administration of the various aerosols used in this study, patients were instructed to exhale forcibly, then to make a maximum inhalation and finally to hold their breath for a few seconds before exhaling. Vital-capacity measurements were made in the usual manner, and tracings of the expiratory curves were made on a moving drum. Care was taken to ensure maximum effort on the part of the patient. Maximum ventilatory volume was determined by the method of Hermannsen, which has been discussed in detail by Courmand, Richards and Darling.⁸ A 9-liter Benedict-Roth type of metabolism apparatus was used, equipped with special low-resistance valves and with the container for soda lime removed. Computation of results was simplified by the addition to the machine of a recording ventilometer that measured inspiratory volume only.⁹ A maximum ventilatory effort was made for fifteen seconds with the patient choosing his own rate and depth of respirations. Normal values for this method are approximately 150 liters per minute for male and 100 liters per minute for female subjects.

RESULTS

Clinical Use of Isuprel

Thirty asthmatic patients were supplied with isuprel in a concentration of 0.5 per cent to be administered with a hand nebulizer at home. Ten of the 30 patients using the drug at home obtained excellent relief, 14 obtained good relief, 3 obtained fair relief, and 3 obtained practically no relief.

Ten of these 14 patients classified as having received good relief with isuprel stated that this was true only when the attacks of asthma were not severe. While under our observation and using isuprel at home, 7 of these patients developed severe asthma and required hospitalization. In this group 3 other patients, although they were not hospitalized, developed severe asthma with no benefit from isuprel and had to be treated by other measures. We could not determine why these changes occurred, but the severity of the asthma may have been the determining factor.

In addition to the 7 patients who had been using isuprel at home before hospitalization, there were 5 patients with severe asthma who received isuprel for the first time in the hospital. Of these 12 patients, 10 required, in addition to isuprel, intravenous injections of aminophylline, repeated doses of sedatives including demerol, infusions of glucose and saline solution, epinephrine and in some cases oxygen with or without helium.

The patients were not encouraged to continue using isuprel when repeated administration gave only very brief and incomplete relief. We are aware that much more intensive and prolonged administration of isuprel aerosol has been reported to be successful under these circumstances. When continued administration failed to produce subjective

or objective improvement in the asthma of our patients, we abandoned this method of treatment and relied upon the procedures mentioned above. Patients in whom isuprel aerosol had become ineffective in relieving the more severe attacks of asthma frequently found that relief with isuprel was obtained from milder attacks occurring subsequently.

Two patients with severe asthma died unexpectedly. The cause of death appeared to be asthma. We were unable to determine what part, if any, isuprel played in these cases. They are presented in detail below.

CASE REPORTS

CASE 1 A 22-year-old married woman, 6 months pregnant, had been admitted to the Massachusetts Memorial Hospitals five times between March and July, 1947, because of severe bronchial asthma. Since early childhood she had suffered with hay fever in the summer and autumn. At the age of 12, during the ragweed season, she had her first attack of asthma, after which she had asthma perennially, with aggravation of symptoms during the pollinating seasons. On several occasions skin tests had shown positive reactions to cat hair, ragweed, birch, oak, grasses, beef, lobster and walnuts. Over the course of years she had used ephedrine, epinephrine, aminophylline, potassium iodide and barbiturates. She had also received injections of pollen extracts.

Early in 1947, when she was 2 months pregnant, she was seen because of a severe attack of asthma and given isuprel for the first time, to be used by inhalation. This preparation was very satisfactory, and relief lasted from hours to days. Weeks later, however, as the attacks of asthma became more continuous and severe, isuprel became less effective, producing relief lasting only minutes. The patient also failed to respond to repeated large doses of epinephrine and responded only to aminophylline given intravenously. Finally, relief obtained by intravenous injection of aminophylline was incomplete and transitory, and she was hospitalized on June 9, 1947.

Physical examination was not remarkable, except for moderate respiratory distress with a nonproductive cough, wheezes throughout both lung fields and a palpable uterus at the level of the umbilicus.

The blood Hinton reaction was negative, and there was no anemia. Examination of the blood revealed a white cell count of 12,700, with 9 per cent eosinophils.

The asthma was controlled with intravenous injections of aminophylline, epinephrine administered subcutaneously, isuprel by inhalation and barbiturates at bedtime. The patient was discharged on July 3. Subsequently, she continued to have mild asthma, for which she used isuprel repeatedly.

The patient was last seen on the evening of July 9, when she appeared well. Shortly after midnight, because of asthma, she gave herself four subcutaneous injections of epinephrine, and during the following morning and afternoon additional injections of epinephrine were taken, the exact number of which is unknown. For sedation during the night of July 9 she apparently took a total of 0.4 gm (6 gr.) of nembutal, and she may have taken some phenobarbital as well. During this time she continued to use isuprel. Her husband saw her at noon on July 10, and except for a rapid pulse, he did not find cause for alarm. Her mother saw her last about 3:50 p.m., when the patient did not appear in any distress. She went upstairs, and the mother followed about 5 minutes later upon hearing a thud. She found the patient lying on the floor, cyanotic, and breathing with great difficulty. She could not be aroused. Fifteen minutes later she died. Permission for autopsy was not obtained.

CASE 2 A 32-year-old married man was admitted to the Massachusetts Memorial Hospitals on April 19, 1947, complaining of continuous asthma of 2 weeks' duration. His maternal aunt had asthma, and his brother had hay fever. He had had hay fever and bronchial asthma in the fall for 10 years. Treatment with ragweed-pollen extracts had given moderately good results. The asthma had been easily con-

trolled by small doses of ephedrine or epinephrine by injection. Skin tests performed in the fall of 1946 gave positive reactions to many pollens, animal danders and foods. One month prior to admission to the hospital he developed urticaria, which did not respond to epinephrine or benadryl, but finally cleared for no apparent reason.

Two weeks prior to admission he began having severe attacks of asthma with no response to ephedrine, epinephrine or aminophylline. At that time he was given isuprel for inhalation, which gave fairly good relief, sometimes lasting 1 or 2 hours. Gradually, however, this preparation became less and less effective, and the severity of the asthma increased so that finally he had to be admitted to the hospital.

Physical examination revealed a well developed and well nourished man in no acute distress who was wheezing moderately and appeared slightly apprehensive. Wheezes and squeaks were heard throughout both lung fields.

Examination of the blood showed a white-cell count of 7600, with 67 per cent granulocytes and 3 per cent eosinophils. The hematocrit was 48 per cent, and the hemoglobin was 15.7 gm per 100 cc. The urine was normal, except for the slightest possible trace of albumin. X-ray study of the chest revealed slight emphysema.

Because of increasing asthma, the patient received repeated injections of epinephrine, which gave little relief. He also received aminophylline intravenously, to which he responded poorly. Aerosolized isuprel produced slight relief for brief periods. The asthma continued to increase in severity, and the patient became dyspneic and cyanotic.

On the 2nd day in the hospital, late in the afternoon, he complained of marked shortness of breath and he was apprehensive. He received ether in oil by rectum, but because of lack of co-operation less than 30 cc was given. He became comatose and remained so for about 2 hours until suddenly, at about 7:00 p.m., he changed color and the respirations became gasping in nature. Artificial respiration, as well as intracardiac injection of epinephrine, was given to no avail. The patient was pronounced dead at 7:15 p.m.

At post-mortem examination* the heart weighed 355 gm. The endocardium was not remarkable, except for the anterior cusp of the mitral valve, which presented a small rectangular plaque of atheroma. The myocardium showed no evidence of fibrosis or infarction. The coronary arteries were palpable in their proximal few centimeters. There was a moderate degree of atheromatous change in the left and right coronary arteries and in the proximal few centimeters of their descending branches. The maximum amount of stenosis amounted to 50 per cent of the lumen. There was no evidence of coronary thrombosis or coronary occlusion.

The lungs together weighed 1760 gm. They were obviously bulky and voluminous. Their color was light pinkish yellow, with a faint reddish tinge that became more prominent in the lower lobes. The consistence of the lungs was quite rubbery, and they pitted easily on pressure. Moderate pressure produced deep pits, which disappeared slowly. Crepitation was elicited throughout but felt slightly reduced, and the normal spongy texture of the lungs was not felt. The trachea and bronchi contained a moderate amount of whitish, mucoid, very frothy material that did not occlude the lumens. The secondary branches of the major bronchi were completely occluded by bright-yellow, purulent, rather tenacious material, which formed plugs. In the smaller bronchi the plugs became firmer in consistence and assumed a brighter yellow appearance. These were found in perhaps half the bronchi and small branches in all lobes. On cut surface, the color of the parenchyma in all lobes was a light red, with tiny pinhead-sized, darker red mottled patches scattered throughout the lobes. The pulmonary arteries were dissected and found free from thrombus.

The microscopical findings of asthma were striking. The bronchi and bronchioles showed some or all of the following changes. The lumens were partially filled with mucoid exudate, in which were embedded numerous desquamated epithelial cells, lymphocytes, eosinophils and bacteria. The epithelium *in situ* was often reduced to a layer one cell in thickness. Occasional squamous metaplasia was seen. Frequently, the mucosa was infiltrated with neutrophils and eosinophilic polynuclear leukocytes. The basement membranes were thickened and hyalinized and their refractile appearance was striking. The submucosa was densely infiltrated with lymphocytes and large mononuclear leukocytes.

*Performed by Dr. Israel Diamond.

Scattered among these cells were many neutrophils and eosinophilic polynuclear leukocytes. The inflammatory infiltrate extended into the bronchovascular connective tissue and very frequently formed a collar around small blood vessels. The infiltration also extended into the mucous glands in the bronchial walls. The glands were numerous and prominent. In many of the walls, the muscle bundles were thickened and very prominent. The bronchial and bronchiolar lumens were never completely occluded by exudate, although a few bronchioles were seen that were almost occluded by masses of eosinophils. No Curschmann spirals or Charcot-Leyden crystals were found.

The atria and alveoli were markedly distended in most areas. They were empty, except for an occasional large mononuclear anthracotic phagocyte or a few red blood cells. Very occasional patches of atelectasis were found. The alveolar walls were rather diffusely infiltrated with neutrophils and eosinophilic polynuclear leukocytes.

The elastic-tissue stains showed marked fragmentation of elastic fibers in the lamina propria of the bronchi. In a few areas, the elastic tissue had disappeared altogether. The refractile, thickened basement membranes were striking in these preparations. The elastic-fiber proliferation in the intima of some of the arterioles and small arteries, with resulting thickening and narrowing of the lumen, was prominent. Many of the arteries showed reduplication and fragmentation of the elastic laminae.

VITAL CAPACITY IN SPONTANEOUS ASTHMA

Observations were made in 23 subjects with spontaneous asthma. The vital capacity of each subject was determined, and any change after inhalations of isuprel was observed. An increase in vital capacity occurred in every case, and this was usually associated with subjective sensations of relief. As a rule the physical signs of asthma decreased, but in 1 case they increased in spite of a rise in vital capacity and a reduction in the subjective sensation of asthma. In most cases in which small increases occurred, the vital capacity was close to the maximum vital capacity for the patient, as judged by values obtained at periods when no asthma was present. One exception was a patient who was followed during a period in which her symptoms were especially severe. Her maximum vital capacity had been observed earlier to be 2700 cc. On the present occasion her vital capacity was 1500 cc., and after fifteen inhalations of isuprel, it was 1550 cc. The subsequent intravenous injection of aminophylline likewise failed to increase the vital capacity.

COMPARATIVE EFFECTIVENESS OF ISUPREL AND OTHER DRUGS

In a few cases there was opportunity to compare the efficacy of isuprel administered by inhalation with that of epinephrine by inhalation (1:100 solution) and injected subcutaneously (1:1000 solution) and aminophylline given intravenously. We recognized the fact that patients may overestimate the efficacy of a new preparation when it is first used and that some of what follows is perhaps best regarded with this tendency in mind.

One subject received five inhalations of epinephrine 1:100 with an increase in vital capacity from 2150 to 2700 cc. A second series of five inhalations caused a further rise of only 50 cc. The subcutaneous administration of 0.3 cc of epinephrine

(1 1000 solution) caused no further increase in vital capacity in a period of ten minutes. Five inhalations of isuprel (1 per cent) then caused an increase to 3050, and a second series of five inhalations caused a further increase to 3700 cc.

In another subject receiving isuprel for the first time, inhalations of the drug (1 per cent) were given repeatedly over a period of thirty minutes. Marked relief of asthmatic symptoms occurred—the best in many weeks. On the following day the inhalations were repeated, but epinephrine (1 100 solution) was substituted for the isuprel without the

by other routes has been limited and is difficult to evaluate.

RELIEF FROM ATTACKS INDUCED BY INHALED ALLERGENIC EXTRACTS

Observations were made in 9 asthmatic subjects in whom asthma-like attacks were induced by exposure to various aerosolized allergenic extracts by inhalation¹⁰⁻¹². As shown in Table 1, the administration of isuprel caused a rapid return of the vital-capacity readings toward normal. In some cases pyribenzamine or atropine had been given with

TABLE 1 *Effect of Inhalations of Isuprel in Restoring the Vital Capacity after Experimental Reduction by Inhalation of Aerosolized Allergenic Extracts*

CASE No.	AGE	SEX	MAXIMUM VITAL CAPACITY	ALLERGENIC EXTRACT	INTERVAL AFTER EXPOSURE TO EXTRACTS	VITAL CAPACITY AFTER INHALATION OF EXTRACT	INTERVAL AFTER EXPOSURE TO ISUPREL	NO OF INHALATIONS OF ISUPREL	VITAL CAPACITY AFTER INHALATION OF ISUPREL
	yr		cc		min	cc	min	0.5%	cc
1	42	F	2,700	Birch pollen	23	1400	6	6*	2125
				Oak pollen	60	1300	4	5	2100
				Birch pollen	34	2150	4	10	2600
				Oak pollen	112	2225	6	11	2700
				Oak pollen	72	1900	112	12*	2700
2	45	F	2 800	Ragweed pollen	20	1750	13	5	2300
3	37	F	2 800	Birch pollen	15	1175	1	10	2225
				Ragweed pollen	124	1900	1/2	5	2125
4	37	F	3 050	Oak pollen	7-67	1100	1	27	2800
				House dust	40	2500	3	5	3150
				Timothy pollen	15	2700	1	5	3050
				Ragweed pollen	49	3300	1/2	4	3700
				House dust	14	3000	1	6	4000
5	22	F	3 700	House dust	9	900	4	5	2400
6	48	M	4 000	House dust	17	3650	1/2	5	4700
7	48	F	2 550	Birch pollen	35	3750	1/2	5	4450
				Ragweed pollen	27	3650	6	5	4300
				Ragweed pollen	17	3500	1	5	4400
				Oak pollen	20	3700	5	5	4100
				Ash pollen	9	1700	4	6	2650
8	38	M	4 500	House dust					
9	15	M	3 100						

*1 per cent isuprel solution administered

†Inhalations of isuprel given over a period of 52 minutes

patient's knowledge. Little relief occurred, and the patient was greatly disappointed. On the third day isuprel was again given, with excellent relief. No vital-capacity studies were made in this patient.

Although most patients who used both epinephrine and isuprel as aerosols stated that the latter was consistently superior, 4 patients stated that epinephrine was as good as isuprel or better, after having had considerable experience with both. The epinephrine preparation used in some cases was a proprietary product containing the drug in a concentration of 2 per cent.

Aminophylline

On numerous occasions patients who were admitted to the hospital for treatment of asthma received both isuprel by inhalation and aminophylline intravenously in doses of 0.25 or 0.48 gm. Although no studies of vital capacity were made, the very definite impression was obtained that aminophylline injected intravenously was superior to isuprel for the treatment of severe asthma. Subjective relief was not only greater but also more prolonged. Experience with aminophylline given

a view to possible protection of the patient from the expected decrease in vital capacity or in an attempt to restore the vital capacity after this had been reduced by exposure to an aerosolized pollen extract. Isuprel was effective in every case but 1, whereas intravenously administered atropine was without influence or had a very slight effect and intravenously administered pyribenzamine rarely influenced the vital capacity under the circumstances of the test. Interpretation of results obtained with tests of this kind is complicated by the tendency of the vital capacity to return toward normal without any treatment. However, inspection of the records obtained in these experiments afforded convincing evidence that inhalation of isuprel was chiefly responsible for the observed rapid increases in vital capacity.

EFFECT OF ISUPREL IN PREVENTING THE REDUCTION IN VITAL CAPACITY AND ASTHMA-LIKE ATTACKS DUE TO PARENTERALLY ADMINISTERED HISTAMINE AND METHACHOLINE

Experiments were carried out in which the effect of isuprel administered parenterally on two occa-

sions and by aerosol on another occasion was observed for evidence of any resulting change in the subjects' susceptibility to injected histamine or methacholine as determined by changes in vital capacity.^{5,6}

In 1 subject the resting vital capacity was 3072 cc and the intravenous injection of 0.02 mg of histamine base produced an asthma-like attack with a reduction of 952 cc in the vital capacity. This type of response occurs in the great majority of asthmatic subjects. In twenty minutes the attack disappeared, and the vital capacity was 3062 cc. A dose of 0.1 mg of isuprel was then given intramuscularly, and within two minutes the pulse was bounding and the rate had increased from 80 to 120 per minute. Marked nervousness, palpitation and faintness were experienced, but these symptoms disappeared within ten minutes, and at this time the vital capacity measured 3103 cc. A second injection of 0.02 mg of histamine base produced no subjective or objective signs or symptoms in the chest, and the vital capacity was not reduced. However, other systemic effects of histamine, such as the gaseous taste in the mouth, flushing and headache, were not prevented by administration of isuprel. A third injection of 0.02 mg of histamine base thirty minutes after isuprel induced slight wheezing in the chest, with a reduction of 920 cc in the vital capacity. It was apparent that isuprel blocked the action of histamine in a manner similar to that of epinephrine,¹³ but its action was short-lived. In this subject 0.1 mg of epinephrine produced no side effects and completely blocked the respiratory effects of 0.02 mg of histamine base after thirty minutes, and some histamine-blocking effect was still demonstrable after sixty minutes.

In another subject, with a resting vital capacity of 4253 cc, the intramuscular injection of 6 mg of methacholine induced an asthma-like attack, with a fall of 1003 cc in the vital capacity. In fifteen minutes the attack had abated and 0.06 mg of isuprel given intramuscularly was followed in a few minutes by palpitation, a rise in pulse rate to 170 per minute and a fall in blood pressure to 70 systolic, 60 diastolic, from the previous level of 120 systolic, 80 diastolic. Eight minutes after the administration of isuprel the vital capacity was 4128 cc. A second intramuscular injection of 6 mg of methacholine produced no subjective or objective changes in the chest, nor was there a significant reduction in vital capacity. However, when the dose of methacholine was repeated thirty minutes after the administration of isuprel, the reaction produced was similar to that before the isuprel had been given. Thus, as in the previous case with histamine, the blocking action of isuprel against methacholine was lost within thirty minutes of the administration of isuprel.

In a third experiment, the subject came to the laboratory with a spontaneous attack of asthma. Four vital-capacity tests averaged 2633 cc. In a period of thirty-eight minutes twenty-four inhalations of isuprel were administered without any side effects, and the vital capacity increased to 3688 cc. At this time 0.02 mg of histamine base given intravenously caused a slight decrease in the vital capacity, and fifteen minutes later 3 mg of methacholine given intramuscularly produced no reduction in vital capacity (Fig 1). In previous studies in this

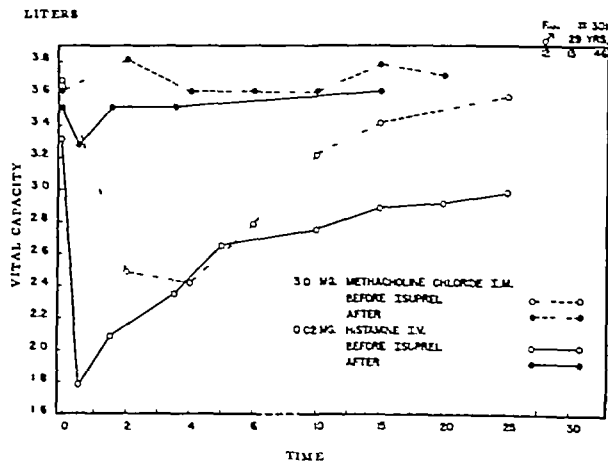


FIGURE 1 Effect of Isuprel Aerosol on the Pulmonary Response to Methacholine and Histamine

The curves with the open circles show the effect of injected histamine base and methacholine on the vital capacity. On another occasion, when twenty-four inhalations of isuprel (1:100 solution) had been given for relief of asthma, the tests were repeated, with the results shown by the curves with solid circles. The time is given in minutes elapsed after the administration of histamine and methacholine.

subject the same doses of histamine and methacholine caused pronounced reductions in the vital capacity.

These studies, though few in number, indicate that isuprel furnishes potent protection against the reduction in vital capacity and asthma-like attacks induced by the parenteral administration of histamine and methacholine. Our experience with the intramuscular use of isuprel is obviously limited, but the short-lived protection afforded against histamine and methacholine together, with the degree of side reactions produced by the drug as compared to intramuscular injections of epinephrine, discouraged us from further studies.

SUBLINGUAL ADMINISTRATION OF ISUPREL

Our experience with the sublingual use of isuprel is limited to observations in 13 patients receiving the drug by this route for relief of symptoms at home and in 2 subjects studied in the laboratory.

Patients receiving tablets of isuprel sublingually at home were instructed to take one tablet containing 10 mg at thirty-minute intervals until relief

(1 1000 solution) caused no further increase in vital capacity in a period of ten minutes. Five inhalations of isuprel (1 per cent) then caused an increase to 3050, and a second series of five inhalations caused a further increase to 3700 cc.

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THE DIAGNOSIS OF CONGENITAL ANEURYSM OF THE PULMONARY ARTERY*

Report of Two Cases

CHARLES T DOTTER, M D,[†] AND ISRAEL STEINBERG, M D[‡]

NEW YORK CITY

THE literature is filled with accounts of dilations or aneurysms of the pulmonary artery. Notable reviews of the literature have been written by Brenner,¹ Boyd and McGavack² and, recently,

(such as syphilis and mycotic infection), congenital defects causing secondary dilatation (septal patency, patent ductus arteriosus, pulmonic stenosis, transposition of the great vessels and other less common lesions), rheumatic mitral stenosis, a variety of chronic pulmonary diseases that may cause



FIGURE 1 Case 1 Conventional Roentgenogram (Frontal Projection)

Note the prominent area of density in the left hilar region

Deterling and Clagett³ Among the factors commonly accepted as causes of pulmonary-artery dilatation and aneurysm are infectious processes

*From the Department of Radiology The New York Hospital-Cornell University Medical Center

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[†]Instructor in medicine Cornell University Medical College assistant resident in radiology The New York Hospital-Cornell University Medical Center

[‡]Instructor in medicine and instructor in radiology (angiocardiology) Cornell University Medical College assistant attending radiologist (angiocardiology) The New York Hospital-Cornell University Medical Center



FIGURE 2 Case 1 Angiocardiogram (Frontal Projection Three Seconds after Injection)

Note that the left hilar shadow is opacified and shown to be a markedly dilated main-stem pulmonary artery and its left branch

pulmonary hypertension, thoracic deformities, cardiac failure and possibly trauma

By our definition, congenital pulmonary-artery aneurysm is an organic, localized or diffuse aneurysmal dilatation of the pulmonary artery that can-

had occurred or until four tablets had been taken in any one day. Of these 13 patients, 3 who were suffering from mild asthma stated that they had obtained excellent relief after taking one or two tablets. Five patients had asthma of moderate severity, and of these, 2 stated that the drug was without effect and the remaining 3 obtained relief of very short duration even with doses as large as 50 mg in two hours. The 5 remaining patients who had severe asthma denied benefit with similar doses.

Two patients with spontaneous asthma were studied in the laboratory. One subject arrived in a mild attack of asthma with an average vital capacity of 2289 cc and a maximal ventilatory volume (M V V) measuring 33.4 liters per minute. The pulse rate was 66 per minute. A 10-mg tablet of isuprel was given sublingually, and in ten minutes the pulse rate was 72 and the M V V 37.6 liters per minute. Again, two 10-mg tablets were given, and ten minutes later the M V V was 48.0 liters per minute, with a pulse rate of 88 per minute. Thus, in a period of forty-eight minutes during which 50 mg of isuprel was administered by the sublingual route no side reactions were experienced, the pulse rate increased from 66 to 88 per minute and the M V V increased 14.1 liters per minute. Subjective relief of the asthma was also experienced. At the end of this period twelve inhalations of isuprel were followed by an increase in M V V to 54.3 liters per minute and the vital capacity was 2874 cc.

In the other subject, spontaneous asthma was present and the M V V measured 45.0 liters and the pulse 120 per minute. At ten-minute intervals a tablet containing 10 mg of isuprel was placed under the tongue until 70 mg had been given. The pulse rate gradually decreased to 104 per minute, and the M V V increased to 65.8 liters per minute. When eight inhalations of isuprel were given, however, there was a rapid increase in M V V to 75.2 liters per minute within ten minutes.

These two experiments suggest that isuprel was not very effective when administered by the sublingual route, except perhaps with large doses. No side reactions were experienced with doses of 50 and 70 mg respectively despite the fact that palpitation and tachycardia were noted after intramuscular doses of the drug as low as 0.1 mg. We recognize the possibility that the physical characteristics of the sublingual tablets and the success patients may have in preventing themselves from swallowing while holding the tablet under the tongue are important factors in the results obtained in studies of this kind.

SIDE EFFECTS

Administration by Aerosol

Only 2 patients in this series of 30 asthmatic subjects experienced symptoms that might reason-

ably be attributed to inhalation of isuprel. In each case nervousness, tachycardia and palpitation were experienced, lasting only a few minutes. In 1 case this followed fifteen inhalations of isuprel (1:100 solution), and in the other, these symptoms followed repeated groups of five to ten inhalations of isuprel (1:200 solution) at short intervals. Both patients used isuprel on other occasions without difficulty.

Sublingual Administration

No side reactions other than a bitter taste were observed in the 15 patients receiving tablets containing 10 mg of isuprel in amounts up to 70 mg within a period of an hour or more. A normal subject receiving one 10-mg tablet sublingually experienced flushing and headache with slight malaise lasting about an hour.

Parenteral Administration

In 5 cases in which isuprel was given subcutaneously or intramuscularly, 2 of which were described above, side reactions were observed. These were tachycardia, palpitation and nervousness in all cases, a fall in blood pressure in 1 case and pallor, nausea and a rise in blood pressure in another. These reactions were not associated with any change in the lung that could not have been readily obtained with isuprel administered by aerosol or with other agents causing fewer or no side effects.

SUMMARY

Isuprel, 1-(3', 4'-dihydroxyphenyl)-2-isopropylaminoethanol, was administered to asthmatic subjects in the outpatient clinic, on the wards and in the laboratory. In most cases the drug was given as an aerosol, but some observations were made in which the drug was given by the sublingual and subcutaneous routes.

The drug given as an aerosol was very effective in relieving mild or moderately severe asthma and appears to be the most effective agent available for self-medication. However, in severe and prolonged attacks of asthma, the drug was far less satisfactory. In certain cases other medications, particularly intravenously administered aminophylline, were required. With recovery, isuprel was again effective in the control of milder attacks. Side effects were uncommon with the doses used in the study.

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its greatest superoinferior dimension, and was best seen in the lateral projection. The remainder of the visualization was entirely unremarkable. There was no evidence of septal defect, patent ductus arteriosus, pulmonic stenosis or other congenital cardiac abnormality. The patient continues to be asymptomatic.

CASE 2 A 50-year-old housewife with an otherwise unremarkable past history was thought to have had tuberculous cervical lymphadenitis at the age of 44, evidenced by a painless swelling beneath the left mandible, which disappeared after the aspiration of sterile white fluid containing a moderate number of leukocytes. Culture for tubercle bacilli was negative. At that time x-ray examination of the lung fields was negative, but a prominence in the left hilus was interpreted as tuberculous hilar lymphadenopathy. Over a 6-year period there was no detectable change in the appearance of the left hilar shadow, and angiocardigraphy was then done to rule out the presence of abnormality of the pulmonary artery. At the time of visualization, the patient was asymptomatic.

Physical examination revealed an apparently healthy woman. A few small lymph nodes were felt in the cervical regions, but these were not thought to be significant. Auscultation of the heart revealed the presence of a blowing Grade III systolic murmur in the second and third intercostal spaces to the left of the sternum. The pulmonic second sound was accentuated. There were no other murmurs. The

and both main branches of the pulmonary artery that measured 60 mm in its greatest superoinferior dimension (measured in the lateral projection). The remainder of the contrast study was entirely unremarkable and failed to show evidence of associated congenital anomaly. The patient is



FIGURE 5 Case 2 Angiocardiogram (Frontal Projection Three Seconds after Injection)

Neo-iodopax outlines a dilated main-stem pulmonary artery and its left main branch, which make up the left hilar shadow.

remainder of the physical examination was unremarkable as were laboratory studies, including a complete blood count and Wassermann test. An electrocardiogram showed slight left-axis deviation.

Conventional chest roentgenogram revealed an apparently normal heart and clear lung fields. In the middle portion of the left cardiac border, a prominent, convex shadow that extended out into the left lung field (Fig 4) was seen. On fluoroscopic examination, this was found to have an expansile systolic pulsation. In the lateral projection, a rounded area of density was observed in the mid-hilar region.

Angiocardiography in frontal and lateral projections (Fig 5 and 6) outlined an aneurysmal dilatation of the main-stem



FIGURE 6 Case 2 Angiocardiogram (Left Lateral Projection Three Seconds after Injection)

The right ventricle, pulmonary conus and pulmonary artery and its left branch are well shown. Note the aneurysmal dilatation of the main-stem pulmonary artery and its left branch.

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DISCUSSION

An attempt has been made to state the diagnostic criteria for congenital aneurysm of the pulmonary artery. This diagnosis is made by the demonstration of aneurysmal dilatation and by exclusion of the known factors causing such dilatation. Since the assumption is generally accepted that the condition is a true congenital malformation, the term "idiopathic" cannot be applied to it. It is suggested that the condition be termed congenital pulmonary-artery aneurysm, the title implying the presence of an uncomplicated or isolated congenital aneurysm.

The 2 cases reported above fulfill the criteria for this diagnosis. Both patients were asymptomatic, and it is assumed that symptoms would be caused by congenital pulmonary aneurysm only when the aneurysm was of sufficient size to produce compression of adjacent structures. Taussig⁵ reports such a case. Surgical intervention in this condition is contraindicated.

SUMMARY AND CONCLUSIONS

The diagnosis of congenital pulmonary-artery aneurysm may be made in the presence of an

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angiocardigraphic study of the normal pulmonary artery has made possible the more accurate evaluation of abnormal findings.⁷ Over a period of eleven years, angiocardigraphic visualizations on more than 650 patients have been accomplished. Of these cases, the clinical and roentgenologic features of 2 allow their classification as congenital pulmonary-artery aneurysms.

CASE REPORTS

CASE 1 A 34-year-old truckman was referred for angiocardigraphy in 1941 because of a prominence at the left hilus seen in a routine preinduction chest roentgenogram. The past and family histories were unremarkable, birth and development had been entirely normal. At the time of examination he was employed as a truckman and experienced no difficulty in doing manual labor. He recalled that he had been refused a job at the age of 22 because a chest film had shown "something around the heart." There was no history of rheumatic fever, and venereal disease was denied.

Physical examination revealed a well developed man whose only significant findings included an accentuated pulmonic second sound, a systolic murmur at the third left



FIGURE 3 Case 1 Angiocardiogram (Left Lateral Projection Three Seconds after the Beginning of Injection)

Superior vena cava, right atrium and superimposed right ventricle, pulmonary artery and left branch are well shown. Note the aneurysmal dilatation of the main stem and left pulmonary artery.

considered to represent congenital conditions. It is difficult to state the dividing line between simple and aneurysmal dilatation of a vessel. Since histologic examination cannot be made during life, and since the vessel wall in congenital aneurysm of the pulmonary artery would probably resemble the normal structure histologically, size remains the most effective criterion. For practical purposes, we refer to a major diffuse dilatation of an artery as aneurysmal. If the dilatation is sharply localized, it is referred to as an aneurysm.

Simple isolated aneurysmal dilatation of the pulmonary artery has been called "idiopathic."^{4, 5} Actually, it is no more idiopathic than a septal defect in that both conditions are true congenital malformations. Angiocardiography has made it possible to delineate pulmonary-artery lesions accurately and to exclude many of the more frequently encountered causes of dilatation.⁶ An

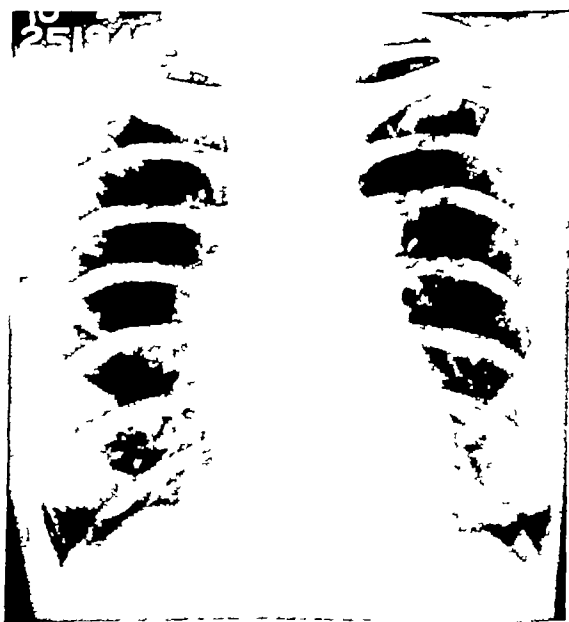


FIGURE 4 Case 2 Conventional Roentgenogram (Frontal Projection)

Note the prominent left hilar shadow which was erroneously interpreted as enlarged hilar lymph nodes.

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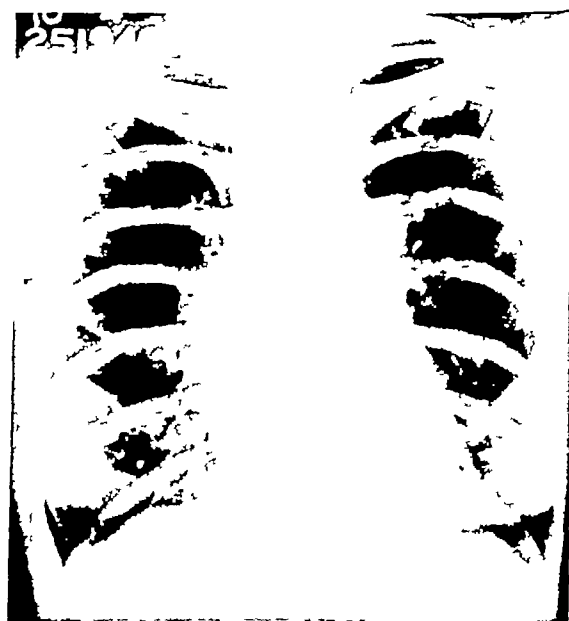


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iodine' and then alcohol. The skin, subcutaneous tissues and periosteum are infiltrated with novocain in a small area just below the iliac crest. The bone-marrow needle is then pushed into the ilium distal to the crest (Fig 1). One usually feels a distinct sense of "give," at which time the stilet is removed, a 10-cc dry syringe is attached and a small amount (0.1 to 0.3 cc) of bone-marrow material is aspirated. Smears are then made directly on specially cleaned glass slides, which are tilted so that most of the blood in the material becomes separated from the flecks of marrow that remain attached to the slide. Then, with the use of the end of another slide, a small portion of the marrow is picked up and smeared gently, with as little pressure as possible, on a third slide. Staining is carried out with a combination of Wright and Giemsa stains.

The *spinous-process puncture* is performed with the patient lying face downward, rather than in the sitting position as recommended by Loge.³ This seems preferable for several reasons. Firstly, the necessary pressure can be more readily employed in the downward than in the horizontal plane. Secondly, the patient lies in a relatively fixed and more comfortable position and cannot be readily moved by the pressure applied. Finally, although the spinous process may be less prominent in the prone than in the sitting and flexed positions, it is easier to isolate and define individually. These reasons are particularly valid in the child. We have utilized a variety of spinous processes and have found that the lower thoracic vertebrae and the lumbar vertebrae are most satisfactory. The patient is prepared with iodine and then alcohol. The spinous process to be utilized is grasped on either side with the thumb and forefinger of the left hand, and the skin, subcutaneous tissue and periosteum are infiltrated with novocain. The bone-marrow needle is then introduced perpendicularly to the process, and after the sense of "give" is felt a syringe is attached and the material withdrawn (Fig 2).

RESULTS

In adults, bone-marrow punctures using multiple sites were performed in 31 patients. Spinous-process punctures alone were done in 25 additional cases. Of the patients with multiple punctures, 3 had sternal, iliac-crest and spinous-process punctures. Comparison of the results obtained with multiple punctures showed surprisingly similar findings, both in the general appearance of the marrow on microscopical study and in the differential counts. Occasionally, marrow was obtained from one site, when another yielded a dry tap. In 3 of our adult cases, multiple punctures revealed hypoplastic or aplastic marrow in three different areas. In 2 of these cases the finding was verified by trephine biopsy. Because of these highly comparable results in different areas, we now utilize

the various sites interchangeably when multiple punctures are performed.

Spinous-process punctures were performed in 25 infants and children ranging from two months to twelve years of age. In 5 children two punctures were done. The iliac-crest puncture was performed in 8. Ten patients had both sternal and spinous-process punctures, 2 patients had sternal, spinous-process and iliac-crest punctures, 2 had iliac-crest and spinous-process punctures, and 1 had a tibial puncture in addition to punctures of the sternum and of a spinous process.

Of the 13 patients who had punctures at multiple sites, comparable results were obtained in 10

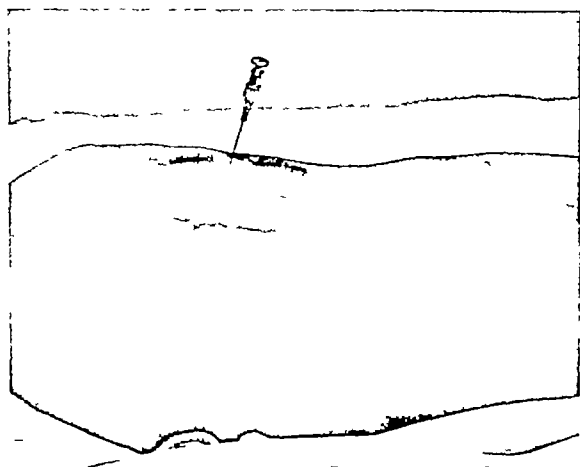


FIGURE 2 Spinous-Process Puncture of an Upper Lumbar Vertebra in an Eight-Year-Old Child, Showing the Position of the Needle (Gauge 18) at the End of the Puncture

In the other 3 cases a diagnosis was made only when multiple punctures were performed. These cases are presented briefly, as follows:

R C, an 11-year-old child, had possible aleukemic leukemia. Sternal puncture yielded a dry tap. Spinous-process puncture produced a small amount of very thick marrow showing an almost pure culture of lymphoblasts. Apparently, the marrow cavity was packed with very thick marrow, which resisted aspiration. It is possible that a second sternal puncture would have revealed similar findings, but the patient was spared this second puncture of an already sensitive sternum by performance of aspiration at an alternate site.

R H, a 2-month-old infant, had thrombocytopenic purpura. Tibial puncture yielded no marrow, and two sternal punctures produced very dilute material, suggesting a hypoplastic marrow as the cause of the purpura. A spinous-process puncture revealed an essentially normal marrow, and the infant subsequently made an uneventful recovery. The final conclusion was that the purpura had been of infectious origin.

D M, who was 3 years and 4 months old, was studied for possible leukemia, aleukemic variety. A sternal puncture and two spinous-process punctures revealed no marrow material. Puncture of the right iliac crest produced material that showed marked infiltration with early lymphoid cells,

aneurysm or aneurysmal dilatation of the pulmonary artery that cannot be accounted for by associated congenital or acquired factors capable of causing pulmonary-artery dilatation

Pressure studies by cardiac catheterization should be carried out whenever possible. The presence of an abnormally high pulmonary-artery pressure must be considered evidence against a congenital pulmonary-artery aneurysm. These studies will be conducted in Case 2.

Angiocardiography adequately demonstrates the nature of the dilatation and aids in excluding other causes of such dilatation.

It is suggested that the term "idiopathic" is misleading and should not be applied to a condition of congenital origin.

Two cases fulfilling these diagnostic criteria are presented

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MULTIPLE SITES FOR BONE-MARROW PUNCTURE, WITH PARTICULAR REFERENCE TO CHILDREN*

JACK J. RHEINGOLD, M.D.,† LOUIS WEISFUSE, M.D.,‡ AND WILLIAM DAMESHEK, M.D.§

BOSTON

EXAMINATION of the bone marrow in hematologic disorders by means of puncture aspiration has become in this laboratory and in many

Blitstein¹ and Rubenstein² have stressed the value of the iliac-crest puncture, and more recently Loge³ and Huss, Gilbert and Liebow⁴ have advocated the spinous process as a site for obtaining a specimen of the bone marrow. Since alternative sites are often desirable we have investigated their value during the past year. Our observations in adults confirm those of the above investigators that essentially similar material is obtained from the various sites taken simultaneously. More recently we have applied the same technique in infants and children and have found that iliac-crest and vertebral punctures are especially valuable in these groups. In infants particularly, the sternal-marrow cavity is quite shallow, and the possibility of perforation into the mediastinum, although remote, is always present. Puncture of the tibial marrow in older children is often unsatisfactory. Furthermore, spinous-process puncture is often preferable for psychic reasons, since the child cannot see the activities associated with the procedure and consequently becomes less alarmed.

METHOD

The same type of stiletted needle is used for the iliac-crest and spinous-process punctures as previously used for the sternal approach.⁵ The needle has a total length of 6.7 cm. and a shaft of 3.3 cm. For *spinous-process puncture* particularly in infants, a No. 1 gauge needle of the above dimensions is preferable. In infants and in young children, light anesthesia as obtained with a few whiffs of ethyl chloride is often useful.

The *iliac crest puncture* is performed after the area about the iliac crest has been prepared with

*This needle ordinarily supplied as No. 16 gauge may be purchased from the Hub Needle Company, Boston, Massachusetts.

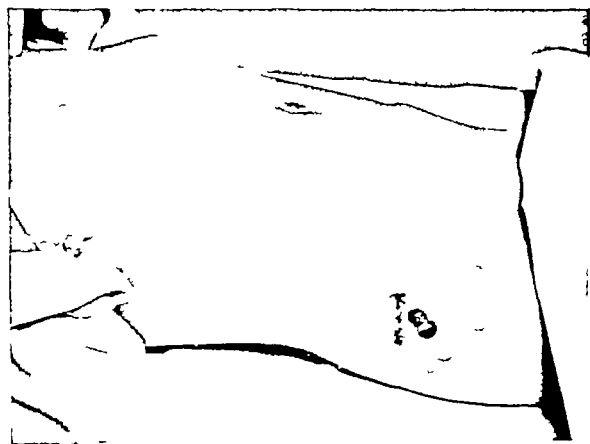


FIGURE 1 Iliac-Crest Puncture, Showing the Position of the Needle (Gauge 16) at the Termination of the Puncture

others a routine study that is often invaluable in diagnosis. Although the sternum is the usual site of such puncture, several investigators have suggested other areas. Thus Van den Berghe and

*From the Ziskind Laboratories (Hematology Section), New England Medical Center, and the Department of Medicine, Tufts College Medical School.

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‡Clinical instructor in medicine, George Washington University School of Medicine, Washington, D. C., formerly fellow in hematology, Joseph H. Pratt Diagnostic Hospital.

§Assistant, Department of Medicine, Long Island College of Medicine, formerly fellow in hematology, Joseph H. Pratt Diagnostic Hospital.

¶Professor of clinical medicine, Tufts College Medical School, hematologist, Joseph H. Pratt Diagnostic Hospital, consulting hematologist, Boston Floating Hospital.

MEDICAL PROBLEMS OF OLD AGE*

ROBERT T. MONROE, M D †

BOSTON

EIGHT years ago, a geriatric clinic was established in the Out-Door Department of the Peter Bent Brigham Hospital in Boston. Its purpose was to study old people from a fresh point of view in an academic atmosphere. It sought to define the medical problems imposed by age. Are diseases in old people different from the same diseases in younger ones? Are diagnostic problems altered by age? Can useful therapeutic measures and programs be devised? In short, is there a place for geriatrics as a distinct discipline in the medical arts and sciences? This paper is the first report of progress from the clinic.

The location of the clinic excluded attendance by old people of independent means, those too feeble to come, and those in almshouses and private homes for the aged. But there was opportunity to study a few of the first group in private practice and to get information on the rest by association with the Committee on the Care of the Aged of the Boston Council of Social Agencies. Patients who came, though of every kind and condition, proved to be most co-operative and willing to do their part in the explorations. The project has not grown in size, partly because it was curtailed during the war and partly because it has received no financial support except for a few small, unsolicited contributions in the last year. It is still limited to one worker. However, sufficient experience has been gained to show that geriatrics can develop into a real medical specialty and that it is most likely to be developed in clinics where the necessary skills and tools can be fashioned for use by physicians, social workers, nurses, physiotherapists and all who deal with aged persons.

Old age is peculiarly the field of chronic disease. Disabilities and deficits incurred earlier in life are brought along into old age, and new ones appear. Persistent and recurrent diseases, such as peptic ulcer, gallstones, hernia and arthritis, are found in greatest frequency in old age. High blood pressure is observed in the majority of men and women over sixty, and heart disease in some form and degree disables or kills more than 50 per cent of them. Malignant lesions reach their greatest incidence in the aged. These conditions will continue to prevail no matter how much progress is made in particular areas or how long the average span of life

is extended. This accumulation of troubles and our inevitable defeat account for the unhappy view of the last third of life that has always been held by society at large, and for the sense of futility in attempting to cope with its complex situations that most physicians feel. To say, "at your age, what can you expect," absolves the physician from further effort and lets the aged patient conclude that it is all up to him.

The geriatrician holds, however, that this is not sound reasoning. These disabilities come slowly and in varying degrees, so that there is an opportunity for the patient to adjust himself to them, satisfactorily in most cases. It is also clear that even now physicians have enough skill to care for chronic diseases and cardiovascular limitations sufficiently effectively to permit life to be lived at reasonably tolerable levels. Neuropsychiatric disasters are not so unresponsive to treatment as they appear to be. Life ends for many old people as naturally as it began, with little distress, in the midst of full, forward-looking participation in society, with no period of custodial care or sitting on the side-line benches. The geriatrician believes that this happy ending can be achieved by many more.

DETECTION OF DISEASE

The detection of disease in old people is not hard. A thorough search is likely to be only too rewarding. Recognition of the factors that are really producing symptoms, however, many require much insight and geriatric experience. For example, a spinster who for fifty years had made her way as a milliner in a down-town store went to a hospital to seek relief from headaches. Her glasses seemed to be correct. She was found to have high blood pressure. Sclerotic arteries were seen in x-ray films of the skull. She was referred to the neurologic clinic, where the blood pressure, the sclerosis, the headaches and the worries added up to a diagnosis of cerebral arteriosclerosis. She was advised to give up her work, to stop worrying and to sleep on several pillows so that her head would not become congested. She became much worse and had to accept charity. She was referred to the geriatric clinic by her minister. There her headaches were considered to arise from spasm of the erector spinae and trapezius muscles produced by worry and the position of stretch on pillows, and the attacks of vertigo appeared to come from an active carotid sinus reflex. She was advised to sleep without any pillow and to dance, to limber up the neck and to lessen external tension upon the carotid arteries.

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†From the Department of Medicine, Harvard Medical School, and the Medical Clinic, Peter Bent Brigham Hospital.

‡Associate in medicine, Harvard Medical School; senior associate in medicine, Peter Bent Brigham Hospital; chairman, Committee on Care of the Aged, Boston Council of Social Agencies.

and the diagnosis of acute lymphatic leukemia was made. Here again, the dry taps were probably the result of a very thickly packed marrow, which resisted aspiration.

Two cases in this series demonstrate the value of using multiple sites for confirmation of the results obtained from a single puncture. In these patients, aged thirteen and three years and nine months, the differential diagnosis lay between aleukemic leukemia and hypoplastic anemia to explain the pancytopenia. In each case the bone marrow obtained from three sites—the sternum, the iliac crest and the spinous process—showed definite hypoplasia and no leukemic infiltration. In 1 patient further confirmation was obtained by trephine biopsy, which showed a hypoplastic marrow.

DISCUSSION

There are definite advantages inherent in multiple sites for puncture. In such diseases as pernicious anemia, idiopathic thrombocytopenic purpura, multiple myeloma and leukemia, it is often desirable to obtain multiple punctures mainly for the purpose of following the course of the disease or the effects of therapy. When several punctures are performed, not only is the use of multiple sites more readily accepted by the patient but also, with the spinous-process approach, a *group* of possible sites for successive puncture is available. In one of our patients with pernicious anemia of pregnancy treated with folic acid, five successive spinous-process punctures were made at the seventh, eighth, ninth, tenth and twelfth vertebrae, respectively. The patient reported very little discomfort, and an excellent opportunity was afforded to follow the changes in the marrow after therapy.

In patients in whom the diagnosis is in question and particularly when hypocellular marrow preparations are obtained, the use of multiple sites offers a means of confirmation of marrow diagnosis. A hypocellular marrow preparation obtained by sternal aspiration may leave one in doubt whether this represents a hypoplastic anemia or an inadequate sampling. The finding of hypocellular preparations

in all three sites is a very definite indication that hypoplasia or fibrosis is actually present.

The use of alternate sites may provide information that is lacking if only the sternal marrow is examined. Just as biopsy of a lymph node or of the liver or spleen may throw additional light on a diagnostic problem, so, on occasion, spinous-process and iliac-crest punctures provide data that would otherwise be lacking. For example, in a recent case, the sternal and spinous-process punctures yielded normal marrow, but iliac-crest aspiration showed a well defined infiltration with lymphosarcoma cells, thus establishing the diagnosis.

Additional uses of alternate sites often occur, as when a sensitive patient refuses to have a second sternal puncture, when irradiation of the mediastinum has so affected the sternal marrow that interpretation of the findings of the sternal aspiration may be difficult or open to question, when the sternum is unusually tender to pressure (this occurs in a number of hematologic disorders) and, in certain cases of metastatic disorders, when localized bone pain or tenderness is present. By puncture of the bone in the region of the most marked tenderness, the possibility of finding carcinomatous cells is considerably enhanced.

SUMMARY

In this laboratory, in which examination of the bone marrow is believed to be an integral part of hematologic study, the use of alternative sites for bone-marrow puncture has been found to be of definite value. In children, the spinous process and iliac crest are often the preferred site for puncture.

A series of cases is briefly presented to demonstrate the use and value of punctures at multiple sites.

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A generalization that time has strengthened was made early in the geriatric clinic: malnutrition and physical and mental unfitness are present in some degree in almost every person over sixty years of age. Malnutrition sets in with lack of a proper diet, as often from wrong ideas about food as from inability to get it. It can come from poor dentures or none. It can result from anorexia due to sorrow or loneliness or loss of drive. It can be intensified by disease, especially diseases with fever, blood loss or cachexia. There is often the hint that the aged organism needs more of certain food factors, such as vitamin B and vitamin C, than have been considered normal amounts for adults, whether from lack of absorption or lack of utilization. Components of the vitamin B complex now constitute the first thought in the clinic for old people with cramps in the legs at night or with unexplained depressions. The war made us conscious of the extra need for protein in cachexia, in hepatitis and in demineralization of bone. Fortunately, an adequate diet is available to all old people in this country—even to those receiving public or private assistance. It is very difficult to get those to take it who cannot change their habits or make substitutions or find value in being well. But the results are worth all the required patience and humor and ingenuity and preaching.

EFFECT OF DRUGS

A great deal of careful observation must be done before it is known whether and to what degree age alters the dosage and actions of drugs. There is an impression that the saturation and maintenance doses of digitalis, for example, are smaller in old persons than in the young or middle-aged. A high concentration of sulfadiazine in the blood is reached rather quickly on small doses, probably because renal filtration is not as efficient in old age. When morphine is administered one should remember the sensitiveness of the respiratory center. Sedatives should be given with much caution, for bromides tend to produce psychotic states and the barbiturates appear to leave the body slowly. The custom of giving small daily doses of phenobarbital to control nervousness and small nightly doses of some other barbiturate to promote sleep is condemned. By their depressive action the drugs in-

crease the fear of loss of mental competence, and by their accumulative tendency they soon fail to produce a satisfactory period of unconsciousness. These objections do not appear to apply to the salicylates or alcohol.

GENERAL THERAPY

The tools that the geriatrician needs are community projects of many kinds. Old-age clubs where lonely, idle persons can go daily for association, for games, for reading, for dances and for developing hobbies are needed. Several are now in existence in Boston. They are not very expensive, but they demand good leadership to control the cantankerous and to bring out the leaners. The natural places for the many more that are needed are the public schools, which are close to old people in every neighborhood, which are for the most part idle in late afternoons and evenings, and which could become truly community centers. Vacation projects are helpful, for elderly persons need the revivifying effects of a change of scene fully as much as young ones, whether or not they are working. Old people on charity seldom get a chance to leave their meager quarters. Most of those who are independently situated live on too narrow a budget to permit a reasonable stay at an attractive place. The management of a farm here, a boardinghouse by the sea there and a camp by a lake somewhere else would be expensive, even if fees were levied according to means. But the benefits derived would be good therapy. And, since most old people would remain at home, there should be summer day-camp club projects in the city, preferably on a portion of public playgrounds, and under supervision to stimulate participation. An employment service, to define and produce paying situations that are suitable for old people and not unfair to young employees, is needed. There should be experiments in boardinghouses, supervised apartments with part-time housekeeping service, simple nursing homes and the activation of homes for the aged to become homes in the full sense of the word and not merely places for custodial care. Best and most expensive of all is an old-age center where all these activities could be housed, directed and promoted, where there could be a gymnasium and swimming pool for rehabilitation, where there could be varied experiments with re-education toward hobbies or jobs or community service, where there could be a psychologic counseling service to determine the aptitudes and mental maturity level as objectively as possible, and where rich and poor could go to find ways to make their last years mean something.

CONCLUSION

The point of view of the geriatric clinic can be summarized thus. There are two groups of old people. There are the very old, those with such

It took several weeks for her to gather courage to carry out the treatment. When she did, her symptoms cleared up. It took much longer for her to get confidence enough to go back to work. Here one can say that the hypertension and arteriosclerosis were anatomic but not clinical facts.

Much that passes for senility turns out to be merely physical unfitness. This is true of much feebleness, frailty, unsteadiness on the feet, awkwardness, undue fatigue, shortness of breath and slow motion. Very few people carry the ideal of a vigorous state of health long after they have left school and its periods of compulsory exercise behind. They exercise as their jobs require or as their vacations or hobbies lead them. When they retire or are retired, inertia seizes them. As a general rule, men in their working years are more fond of keeping physically fit than women are, but after retirement women maintain themselves better because they adjust themselves more naturally to home life than men do. There is no gainsaying the common knowledge that after sixty there are losses in speed and in endurance. But the experience of the geriatric clinic is clear that much can be accomplished, mentally as well as physically, by simple games (bowling, shuffle board and ring toss) and by dancing to restore the sense of timing and coordination. The clinic patients have responded well when the only available outlet was their own ingenuity and the radio. It is also clear that regular exercise and play have beneficial effects on patients with high blood pressure, hypertensive heart disease, arthritis, emphysema, paralysis agitans and hemiplegia. Here is a field of rehabilitation as exciting and as rewarding as that with war casualties. A great deal is packed into the phrase of Juvenal *mens sana in corpore sano*.

Much that appears to be mental deterioration in old age is not so at all. Perhaps not more than 10 to 15 per cent of old people show organic, irreversible losses of mental functions. Very few people study after their school days, except as their livelihood compels them. Their reading may be limited to newspaper headlines and magazines. When they lose their jobs, they often find themselves too rusty to activate unused aptitudes or restore neglected hobbies and studies, and they drift along idly on daydreams. Or an accident, loss of sight or hearing or locomotion, loss of family or friends or fortune, loss of accustomed reasons for living finds them so concentrated on their misfortunes that they have no attention to give to things that go on around them. Therefore, these things are not remembered, and, since loss of memory is a sign of old age, they are thrust deeper in depression by being made aware of that fact. They depend upon others to remember things or to do tasks that the limitations of old age prohibit, and dependency paralyzes their intellectual output still more. Certain diseases produce flagrant states of psychoses, which clear up when

they are cured or controlled — for example, severe anemia, high fever, severe heart failure and obstructive situations in the urinary tract. The geriatrician is conscious of how important it is for the mental health of his patient that he treat vigorously every interfering ailment and find ways of restoring confident living.

It is appropriate that the old person's chief complaint may have little to do with what really concerns him. Even if it does, there are other complaints and many matters that he needs to talk over with someone. He has outlived the parents to whom he turned in time of trouble. His friends are gone, and now, still the same human being, in the dark about how to pursue his course, or how to find a course to pursue, he must bring himself to turn for advice to younger people, it is equally difficult for younger people to give him an attentive ear — for the pupil to turn teacher. Who is in a better position to give friendly, neutral, skillful, understanding advice than the medical adviser? Here is a tremendous extension of medical responsibility far beyond what can be taught in school or laboratory. But the old-fashioned general practitioner fulfilled this responsibility. It is a burden that practitioners today must recognize and assume if they are to deal adequately with the needs of old people. It takes an endless amount of time, much insight and ingenuity, tolerance and patience. The reward is in making the last third of life worth while to many persons.

A typical problem in geriatrics is illustrated by the first patient referred to the clinic. She was a sixty-eight-year-old Austrian widow who complained of belching of gas and epigastric burning. She had been studied by every medical house officer in the Peter Bent Brigham Hospital in the course of the previous five years, four gastrointestinal series, two barium enemas and two x-ray examinations of the gall bladder were negative, all therapeutic reassurance and diets and medications were of no avail. She sat across a narrow table from the examiner and for an hour and a half described and illustrated her symptoms. Her appearance was not prepossessing, for the motion of her false teeth did not synchronize with the tremor of her head. The examiner, determined not to abandon geriatrics at the first shot, asked questions from time to time — who she was, where she came from, how she lived. Finally, she began to answer them, and for ten minutes she gave a detailed story of her origin and emigration to America, where she stayed first, where she worked, how she met and married her husband, how he had died and how she had subsequently lived. She was asked to return in a week to discuss ways of spending her welfare allowance to better advantage, and it was then pointed out to her that she had not belched in the last ten minutes. "Oh," she said, "that doesn't bother me." And then it dawned upon the examiner that her nervous indi-

gestion was this poor, lonely, dependent woman's only claim to importance. She had no excuse for leaving her tenement except to go to church to the store and to the hospital, where all the specialists were so interested in her. In subsequent visits her habits of living were reviewed, and a girlhood interest in Austrian cross-stitching was revived. At Christmas she exhibited samples of her art in the local saloon, which was the only place in the neighborhood with lighted windows. She continued to need welfare assistance, but no longer complained of gas or burning.

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CONCLUSION

The point of view of the geriatric clinic can be summarized thus. There are two groups of old people. There are the very old, those with such

limitations of body, mind and pocketbook that they need custodial care, these are the ones on whom most attention has been centered and the ones we have in mind when old age is thought of with dismay. But there are also young old people, most of them independent or at work. We must direct our efforts at them. If we do, if we discover means of keeping them at work, if we find ways for them to rehabilitate themselves physically and intellec-

tually, if they are given adequate care in sickness and convalescence, and if they have normal opportunities for play, vacations, social association and community participation and for living, many of them will retain their independence, and the break to custodial care will be of short duration or will not come at all.

270 Commonwealth Avenue

CLINICAL NOTE

CONSERVATIVE TREATMENT IN PLACENTA ACCRETA

REPORT OF A CASE IN TWIN PREGNANCY

SAMUEL P. NORMAN, M.D.*

MALDEN, MASSACHUSETTS

THE abnormal adherence of all or part of the placenta to the uterine wall, so-called placenta accreta, is a complication in obstetric practice that calls for accurate, rapid diagnosis, and perhaps emergency treatment. It is not a common finding, Irving and Hertig¹ record the incidence at the Boston Lying-in Hospital to be 1 in 1956 deliveries. The survey by Phaneuf² reveals a frequency of 1 placenta accreta in 14,622 deliveries. There is only one previous report of placenta accreta occurring in twin pregnancies.³

The dangers of hemorrhage and sepsis in adherent placentas have made immediate hysterectomy the accepted treatment. However, conservative therapy may have a definite place, especially when there is complete absence of uterine bleeding. In the following case of placenta accreta in twin pregnancy the patient was treated without surgical intervention.

Mrs. M. P., a 27-year-old primigravida, whose last menstrual period had begun on July 12, 1947, was admitted to the Malden Hospital on March 21, 1948, in premature labor. Pregnancy up to that time had been normal. The patient was Rh+. Under low spinal anesthesia, a living premature female infant was delivered by Scanzoni maneuver, after a right mediolateral episiotomy. Immediately after the birth of the infant, a large placenta with membranes and cord was delivered intact. At this time, it was noted that the uterus was still large, and within a few moments, a macerated still-born female fetus was delivered along with an umbilical cord about 30 cm in length broken off at its distal end. A second placenta and membranes did not present.

The first placenta was examined very carefully, and no place could be found where the second umbilical cord might have been attached. There was no sign of hemorrhage. After 45 minutes, the uterus was entered in an attempt at manual extraction of the second placenta, but no line of cleavage could be felt. A second obstetrician, called in consultation,

was also unable to find a line of cleavage but did remove a few shreds of membrane. There was still no bleeding, and the patient's condition was good despite manipulation. The blood pressure was 120/70, the pulse 84, and the respirations 20. The flow was normal. Since the fundus was hard, firm and well contracted, all operative intervention was discontinued, and the patient was returned to her bed. On the following morning, the placenta had not been expelled. The patient was not bleeding and her blood pressure, pulse and temperature were normal. Penicillin was administered in a dosage of 100,000 units every 3 hours for 4 days. It was decided to observe her progress for at least 36 hours before considering surgery since there was no apparent indication for hysterectomy. At the end of this period, the patient was in excellent condition. The flow was not excessive, and the uterus was contracted and firm. A final decision against removal of the uterus was made. The patient was discharged 10 days after delivery, after an uneventful convalescence. Post-partum examination 6 weeks later revealed a well healed perineum and a normal fundus. She had a normal menstrual period 8 weeks after delivery.

In this case the question of a placenta succenturiata was considered as well as that of accreta, but pathological examination of the placenta revealed no site where the umbilical cord might have been inserted.

Nearly all writers agree that the treatment of placenta accreta is immediate hysterectomy. However, Schumann⁴ cites special indications for conservative treatment and presents a series of 14 cases with no mortality and 2 subsequent pregnancies. His chief indication for conservative treatment is absence of bleeding.

In considering the fate of the placenta that was not expelled, one must hypothesize that since the fetus was stillborn and the first placenta was very large, the second placenta must have been very small and that, because of its small size, it did not have a sufficient blood supply and therefore degenerated. Secondly, this might have been an increta or percreta type of placenta (Kaltreider classification), which had so grown into the uterine musculature that it could not be removed.

This case was similar to those reported by Schumann.

SUMMARY

A case of placenta accreta occurring in a twin pregnancy with one live infant and one macerated fetus is presented. The patient was treated conservatively and made an uneventful recovery.

300 Ferry Street

*Associate surgeon. Department of Obstetrics and Gynecology. Malden Hospital.

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MEDICAL PROGRESS

CARE OF THE NEWBORN*

STEWART H CLIFFORD, M D †

BOSTON

FOR many years neonatal mortality rates resisted all efforts at reduction. In Massachusetts from 1910 to 1930 the infant mortality occurring from two weeks of age to one year fell over 60 per cent while the neonatal death rate fell but 14 per cent (Fig 1). However, during the past fifteen years there has been a gratifying fall of 32 per cent in neonatal mortality, from a rate of 31 deaths per 1000 live births to a rate of 21. Despite this improvement the first two weeks still remains the most dangerous period in life — 64 per cent of the present infant mortality in the Commonwealth occurs during that interval.

A number of factors have contributed to the recent reduction in neonatal mortality. All people have enjoyed a higher standard of living, with resulting improved nutrition in the child-bearing group and the ability to command better medical care. There have been great advances in the sciences of obstetrics, pediatrics and public health and wide dissemination of this knowledge to the medical profession and general public. The federal Government, through the Children's Bureau, has paid particular attention to the welfare of the newborn, and much of the present success can be traced to these efforts. The district and local health departments have been very active in promoting programs to improve the care of the newborn, with splendid results. Not the least of the factors contributing to the improved status of the newborn has been the rapid shift of the scene of childbirth from the home to the hospital. In Massachusetts during the past year 96 per cent of all births took place in hospitals. While the over-all picture has improved, the shift from the home to the hospital has not been an unmixed blessing but has of itself created new problems, which are considered below.

PRENATAL PROPHYLAXIS

The health and nutrition of the mother from the time of conception on may exert a direct influence on the developing embryo and fetus. The classic animal experiments of Warkany¹⁻³ have demonstrated that maternal diets completely deficient in vitamin A, B or D during the breeding period and the following fourteen days will produce a high incidence of malformation in the young, each vitamin lack producing a different and characteristic type of abnormality. These findings on animals must be applied to the problems of human nutrition with caution since no diet for human beings could be deprived of vitamins to the extent necessary to produce abnormalities in rats. Burke and his associates⁴ analyzed the diets of 216 women observed throughout pregnancy and found in the 36 women on poor diets 8 infants with congenital anomalies whereas but 1 occurred in the group of 31 mothers on good diets.

Infection due to the rubella virus,⁵ occurring early in pregnancy, has been found to cause congenital malformations in the newborn such as congenital cataracts and heart disease, deaf mutism, mongolian idiocy, microcephaly, hydrocephaly and mental retardation. Ingalls⁶ believes that mongolism may be the result of injury to the embryo between the sixth and ninth weeks of life. He contends that agents responsible for this injury may include hemorrhage, threatened abortion, pathologic abnormalities of the uterus and certain acute infections. He suggests that these agents injure the embryo through anoxia, through temporary starvation or through the accumulation of toxic metabolites.

Ingalls states that forty years ago Mall stressed the importance of faulty implantation of a normal ovum in the production of a pathologic embryo and that, at the same time, Stockard concluded that two main mechanisms were involved in ab-

*From the Boston Lying in Hospital and the Department of Obstetrics and Pediatrics, Harvard Medical School.

†Associate in pediatrics, Harvard Medical School, pediatrician, Boston Lying in Hospital, physician and chief of Premature Service, Infants and Children's hospitals.

normal development. In one the abnormality was of germinal origin, producing accidents such as albinism, certain legless conditions and polydactyly. In the other, true monsters arose from normal ova developing under abnormal conditions or under unusual circumstances.

A number of studies have been made on the influence of prenatal factors on prematurity. Ebbs, Tisdall and Scott⁷ found the incidence of miscarriages, premature births and stillbirths to be

of prenatal influences. Studies in this new field of prenatal prophylaxis should bring rich rewards both in reducing the incidence of stillbirths, premature births and congenital abnormalities and in improving the health of the newborn infant at birth.

NATAL PROPHYLAXIS

The present methods of safeguarding the baby during delivery represent one of the greatest achieve-

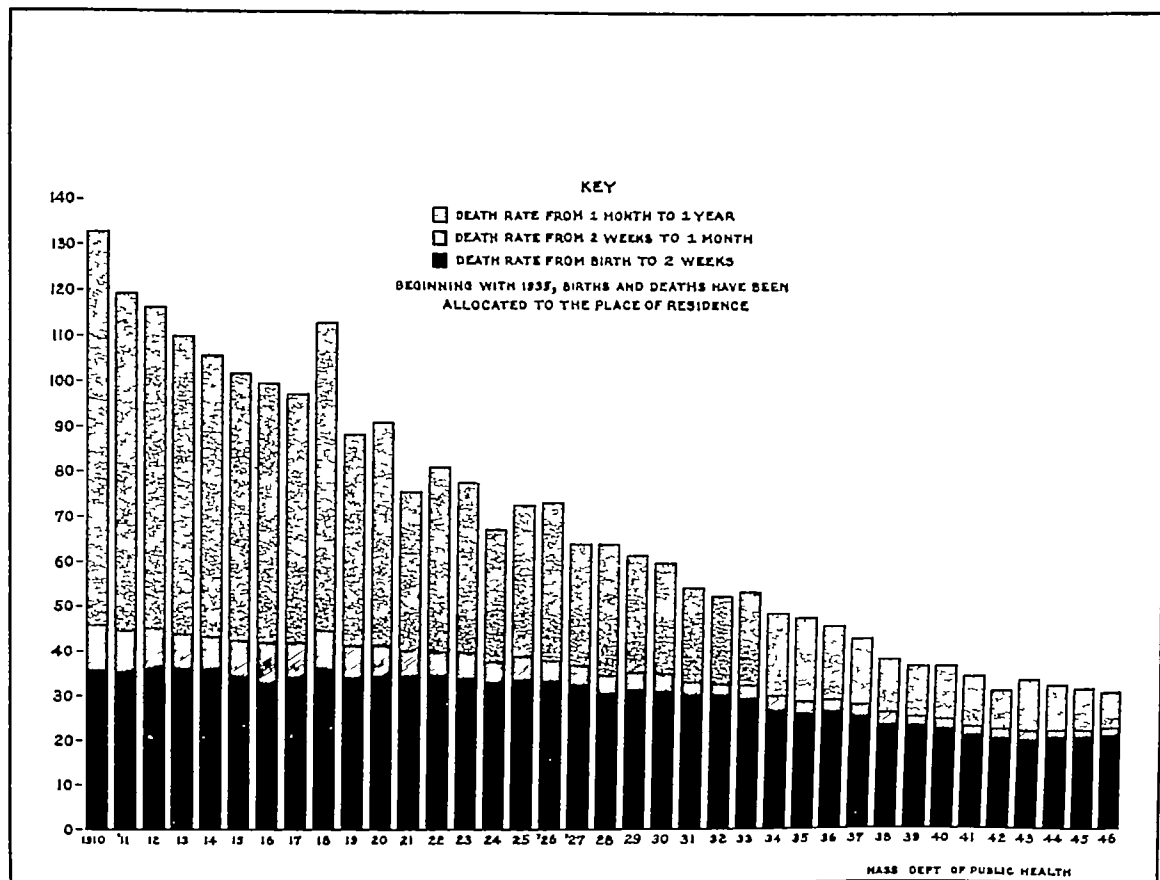


FIGURE 1 Infant Mortality in Massachusetts by Age Groups per 1000 Live Births

greater in a group of women on poor diets. Burke et al⁸ reported that the occurrence of stillborn, premature and functionally immature infants, as well as those with marked congenital defects, was practically limited to a group of mothers whose diet during pregnancy had been inadequate.

Brown, Lyon and Anderson⁹ found the incidence of prematurity significantly increased by maternal illness, severe toxemia, eclampsia, mild bleeding, placenta previa, premature separation of the placenta, acute infections and chronic disorders of pregnancy.

It is thus apparent that many of the problems encountered in the newborn may be the aftermath

of modern obstetrics. The major dangers from which the infant must be protected result from trauma and anoxia.

Serious traumatic injury to the infant during delivery is now practically never seen. One important milestone in the elimination of traumatic injury was the substitution of physiologically sound pressure from above for traction from below. Almost overnight brachial palsies and spinal-cord transections disappeared and gross intracranial hemorrhages became exceedingly rare. Another important step was maternal analgesia that was safe for baby as well as mother. Because of the analgesia the mother was allowed to proceed through labor without inter-

ference, and the incidence of high-forceps and mid-forceps extractions also practically disappeared. The third important milestone in the elimination of traumatic injury was the introduction of x-ray pelvimetry and the following of the progress of doubtful cases by serial x-ray examination. It is possible, but not proved, that the administration of vitamin K to the mother during labor has reduced the incidence of intracranial bleeding.

Protection of the infant from the devastating effects of anoxia is one of the major problems with which obstetricians are confronted today. In this clinic 58 per cent of the deaths among infants, both full term and premature, are the result of anoxia. There are, to be sure, many complications of pregnancy in which serious anoxia is unavoidable and beyond present methods of control. However, some types of anoxia are completely preventable. The use of high concentrations of nitrous oxide or of cyclopropane during labor will inevitably produce severe fetal anoxia. The practice of delaying delivery of the head by direct or indirect pressure to the perineum with or without deep maternal anesthesia is indefensible and extremely dangerous. It is frequently a tragedy that the baby involved in such a procedure survives but with gross neurologic damage.

NEONATAL PROPHYLAXIS

Hospitals have assumed a tremendous responsibility in attempting to provide care for all the newborn infants in the nation. The considerable confusion that surrounds the problem is due to a number of factors: the speed at which the shift from home to hospital took place, the shortage of hospital and nursery beds, the increased birth rate, the demand for care by a private physician and for private and semiprivate rather than ward accommodations, the shortage of nursing personnel, the problem of increasing costs and unbalanced budgets, and the unco-ordinated attempts by the overlapping interested groups of doctors, nurses, administrators and public-health authorities to offer independent solutions for the problem.

The position of the public-health authorities toward the care of the newborn in hospitals is clear. They must represent and protect the interests of the general public by establishing, after consultation with all interested groups, minimum standards and regulations for the hospital care of newborn infants as a basis for the yearly licensing of such obstetric units. They must make sufficiently frequent personal inspections to satisfy themselves that these minimum requirements are being continuously met.

The hospitals themselves should not be content with minimum standards but should strive at all times toward ideal care for their babies. The Committee on Fetus and Newborn of the American Academy of Pediatrics has committees on fetus and

newborn organized in forty-seven states, four Canadian provinces and Hawaii, and each committee is anxious to co-operate with any hospital group in helping to solve its individual nursery problems.

Any hospital seeking to organize and improve its newborn service can obtain valuable assistance from the Manual, *Standards and Recommendations for Hospital Care of Newborn Infants—Full Term and Premature*, prepared by the Committee on Fetus and Newborn of the American Academy of Pediatrics and now in press.

DISEASES OF THE NEWBORN

The major causes of morbidity and mortality in newborn infants, full term and premature, are relatively few—anoxic injuries, traumatic injuries, infections, congenital defects and erythroblastosis. It is of great practical importance that the vast majority of these conditions can be recognized within the first forty-eight hours of life. It would be highly desirable, therefore, if all newborn infants could be closely observed and examined by specially trained nurses and pediatricians, if possible in a special nursery, for the first twenty-four to forty-eight hours of life, before being distributed to their regular nurseries.

By all standards the most important cause of newborn morbidity and mortality is anoxic injury, which alone accounts for nearly 60 per cent of mortality. Anoxia¹⁰ produces progressively congestion, edema, hemorrhage and necrosis in any or every organ and tissue of the body. The combinations of clinical symptoms that may result are almost unlimited. The only treatment that will stop the cycle of anoxic injury is the administration of oxygen. Many newborn infants are immediately placed in an atmosphere of 50 to 60 per cent oxygen as a prophylactic measure even before clinical symptoms have become evident. Undoubtedly, more oxygen than is necessary is used, but it is believed that this procedure has prevented the occurrence or minimized the extent of dangerous complications in an unknown number of infants. All prematurely born infants are routinely placed in an oxygen bed for at least twenty-four hours, and all those with erythroblastosis severe enough to require treatment, and all those with atelectasis are kept in oxygen for four or five days. All babies with a history of fetal distress and all who have required resuscitation are automatically placed in oxygen.

The generalized edema that develops in both full-term and premature infants as the result of anoxia is a very striking finding. It may be a fatal error to start giving fluids too early to such infants in the presence of edema. The added fluid increases the existing edema and may produce serious cerebral and pulmonary complications. It is a fixed policy to give no fluid to premature or full-term infants in the presence of edema. In rare cases

a small premature infant may receive nothing for as long as four or five days. This principle of managing edema was postulated on clinical grounds and has been associated with a further lowering of premature infant mortality to 16 per cent. The work of Smith¹¹ has now given chemical support to this thesis.

Infants with intracranial bleeding,¹² whether due to anoxia or trauma or both, are kept in oxygen, given nothing by mouth for several days and treated by repeated lumbar punctures until the spinal fluid is practically normal.

The birth of erythroblastotic infants may be forecast weeks before term by the appearance of anti-Rh agglutinins in the serum of mothers with a suggestive history and Rh setup. When it is obstetrically advisable these babies are delivered several weeks before maturity. Blood from the infant's umbilical cord is immediately studied for Rh type and the presence of Rh antibodies. If circulating antibodies are demonstrated the infant receives an immediate replacement transfusion with Rh negative blood. Under this routine the mortality from erythroblastosis has fallen from 40 to 10 per cent.¹³ Unfortunately, the incidence of kernicterus has not been reduced by present methods of treatment.

Pediatricians have an increasing obligation to recognize certain congenital defects early in the newborn period since an increasing number can be cured by prompt surgical procedures. Only a few years ago all babies with a tracheoesophageal fistula died—today 8 out of 10 should be completely repaired.¹⁴ Every infant exhibiting an unusual amount of oral mucus immediately after birth should be suspected of having this condition until the contrary is proved. The diagnosis is made by the demonstration of a blind esophageal pouch through the passing of a stiff catheter into the esophagus and the taking of an x-ray film with the catheter in place.

One in every 4 infants with congenital absence of the bile ducts has a condition that may be cured by surgical intervention.¹⁵ It must be remembered that jaundice may be very slight in this condition throughout the newborn period. Every case of even mild jaundice must be considered as a potential congenital obliteration of the bile ducts until proved to the contrary.

Congenital obstruction of the intestine is a relatively common condition in the newborn—including premature infants. Every case of vomiting in the newborn, especially if it begins immediately after birth, must be considered obstruction until disproved. The obstruction may be intrinsic and, if multiple, may be inoperable. It may be due to meconium ileus and require operation or to a meconium plug in the rectum or descending colon and respond dramatically to a simple enema. It may be caused by constriction by short bands of

mesentery associated with malrotation of the cecum or by a volvulus, intussusception, pyloric stenosis or diaphragmatic hernia. A 3-pound premature infant with an obstruction due to an annular pancreas was successfully operated upon on the sixth day of life. The common symptom of obstructions is vomiting, and the diagnosis can frequently be made by a plain x-ray film of the abdomen.

INFECTION

It should never be forgotten that both premature and full-term infants may develop all the types of infection seen in older infants. They are particularly susceptible to infections that may enter through the umbilical vessels. However, at present I am particularly concerned with a relatively new type of infection that has appeared secondary to the concentration of large numbers of babies in common nurseries. Epidemic diarrhea of the newborn has become a public-health problem only during the past fifteen years.

A review of the literature on this condition¹⁶ warrants the conclusion that it is not a pathologic entity but rather a symptom complex that may be caused by a variety of organisms and by at least one and possibly more viruses. The conclusion was reached that many epidemics were caused by glaring errors in nursery technic and by faulty epidemiologic management of the first cases of diarrhea that appeared. It was suggested that simple sound nursery practice could prevent practically every epidemic of diarrhea even in crowded nurseries.

The New York State Public Health Council on January 16, 1948, added a new regulation to its sanitary code designed to control diarrheal diseases of the newborn in nurseries.¹⁷ These regulations were arrived at after consultation with the New York State Medical Society, many individuals and organizations and were written to agree in principle with the recommendations of the Children's Bureau and the Committee on Fetus and Newborn of the American Academy of Pediatrics. The New York Department of Health summarizes the requirements of Regulation 35 as follows: mandatory terminal "sterilization" of formulas in individual feeding bottles with nipple and nipple cap attached, certain principles of isolation, the use of the "suspect" nursery systems for observing infants with suspicious signs of illness, individual care for each infant with his own equipment, adequate space for such care, adequate nursing personnel, smaller groups of infants in each nursery and careful hand-washing by physicians and nurses after coming in contact with any infant.

A similar program was proposed, but not made mandatory, by the Massachusetts Department of Public Health at a series of conferences throughout the Commonwealth in June, 1947. Dr. Roy F.

Feemster, director of the Division of Communicable Diseases, has given me permission to report the amazing sequel of these conferences. In the period from June, 1946, to June, 1947, the Department of Public Health was forced to close the newborn nurseries of 9 maternity hospitals because of outbreaks of epidemic diarrhea. All these outbreaks were serious, with fatal cases in each. From June, 1947, to April, 1948, there was not a single epidemic of newborn diarrhea in the Commonwealth. The Department was called in by 11 hospitals with isolated cases of newborn diarrhea, no nursery was closed, and no deaths occurred in any of the reported cases.

CARE OF THE PREMATURE INFANT

Care of the prematurely born infant is the major problem of the neonatal period. Every hospital can anticipate that 5 or 6 per cent of their expected births will be infants weighing 2500 gm (5 pounds and 8 ounces) or less and that from this small group will come 60 per cent of the newborn mortality.

The Children's Bureau¹⁷ has been a leader in efforts to improve the care of premature infants and is ever ready to assist state and local groups in their problems. Since 1935 the Bureau has had the responsibility of administering grants-in-aid to states for maternal and child health under the Social Security Act. The maternal-health and child-health fund available for state grants amounts to \$11,000,000 per year, half of which goes to states in proportion to their number of live births and must be matched dollar for dollar from state funds. To receive its share a state must submit a plan outlining its proposed program and indicating how it will meet certain requirements of the act. Forty-four states have some activity in relation to premature infants financed from maternal-health and child-health funds. At present 7 states have premature centers now in operation, and 6 more states are in the process of starting such centers. Most of the states concentrate on one, two or three good centers to which premature infants are brought by ambulance.

The details of organizing, equipping and operating a nursery for premature infants are beyond the limits of this discussion and may be found in *Care of Premature Infants*, published by the Division of Maternal and Child Hygiene, Illinois Department of Public Health, in the *Recommended Standards for the Care of Premature Infants*, of the Bureau of Child Hygiene, New York City Department of Health, and in the manual mentioned above that is to be published by the Committee on Fetus and Newborn of the American Academy of Pediatrics.

Methods to protect the premature infant from infection deserve some consideration. If it is granted that for practical purposes all premature infants at the moment of birth are free from infection, it

is a striking fact that in some nurseries infection of premature infants, usually accompanied by diarrhea, is virtually unknown, whereas in other nurseries it is a constant major problem. It is my strong conviction from years of experience with the problem that premature infants born in a hospital devoted exclusively to obstetrics, where the medical and nursing staff have no contact with infected general-hospital patients and no contact with other doctors and nurses caring for such patients, are peculiarly free from infection, with or without diarrhea. Premature infants born in the obstetric ward of a general hospital, even when cared for in a separate nursery, are prone to infection and diarrhea. Premature infants transported to a premature nursery setup in connection with a general pediatric hospital are particularly susceptible to infection and diarrhea. In my own experience the incidence of infection and diarrhea has been sharply curtailed—but not eliminated—in a premature nursery operated as part of a general infants' hospital when each premature infant is kept strictly isolated in a Chapple bed.

As a result of the above experience I recommend that premature centers be located in obstetric hospitals, in an independent building widely separated from a general hospital with a completely independent staff, if in connection with a general hospital—as far away from the children's and infants' wards as physically possible and equipped so that each infant can be kept and cared for in its own air-conditioned unit throughout its entire stay.

CULTIVATION OF A NORMAL MOTHER-INFANT RELATION

McLendon¹⁸ has summarized the cultivation of a normal mother-infant relation as presuming breast feeding, observation by the mother of her newborn child's development, partial care of her newborn infant commensurate with her physical ability, the consequent accumulation of knowledge of her infant's behavior characteristics, particularly in connection with hunger, and confidence in her ability to interpret behavior expressions and to handle them properly.

Macneill¹⁹ points out that the *place* of birth has a definite relation to breast feeding. In Detroit the incidence of breast-fed babies varied from 5 to 6 per cent in one hospital to 69 per cent in another. In Philadelphia a survey in two hospitals revealed a ratio of 24.6 per cent to 83.3 per cent. Common experience indicates that such discrepancies between hospitals exist.

Aldrich²⁰ has summarized the advantages of breast milk as a specific food and the advantages of breast feeding as a technic in child care. In connection with breast feeding he points out that teachers and laymen interested in the emotional problem of children, psychologists, psychiatrists and pedi-

atricians interested in growth and development all emphasize that this form of feeding provides a greater feeling of security to the baby. Through nursing at the breast the baby may gain a feeling of physical continuity with his mother, which as he progresses may lead to the feeling of "belongingness" considered by many psychiatrists to be the first step in the normal mother-child relation. The mother herself may benefit physiologically and psychologically through thus demonstrating her real importance to the infant.

The mother must be "sold" on the idea of wanting to nurse her infant—if possible, during the prenatal period. Many obstetricians begin this process of education at the first prenatal visit. Everyone knows how futile it is to try to convince a young mother that she should nurse her baby if her mind has been made up to the contrary. Aldrich²⁰ states that many psychiatrists consider that if a mother actively rejects the idea of nursing, it is probably unwise to urge it.

The obstetric department, psychiatric consultant and nursing school are experimenting with prenatal clinics on the psychologic preparation of the patient for childbirth in which the importance of future breast feeding is not neglected. It is too early to quote results, but the number of infants completely breast fed on discharge has risen to above 50 per cent.

Real help is needed for reducing the number of breast-feeding failures in willing mothers. Macneill¹⁹ gives an excellent consideration of this problem. He considers some cracked nipples to be caused by the infant's efforts to obtain milk from an obstructed channel, the obstruction persisting unless the tension within the breast is lessened. When the secreting cuboidal cells become flattened by milk pressure, milk production stops. Waller²¹ has shown that the careful and judicious use of stilbestrol in the early stages of increased milk tension relieves the pressure and inhibits the onset of the edema, which becomes the obstructing factor. Waller also claims that the prenatal removal of colostrum through manual expression, by the instructed expectant mother, from about the seventh month of pregnancy on, will facilitate the passage of milk through the breasts and lessen the hazard of engorgement. Macneill¹⁹ advises that injured nipples be treated by the early application of hypertonic compresses to painful nipples and the protection of the injured nipples by a soft, rubber, conforming breast shield until the injury is healed.

All recent authors agree that the "rooming-in" system of infant care and "demand feeding" will contribute materially to successful breast feeding as well as satisfy the other postulates. McLendon¹⁸ has laid down for the cultivation of a normal mother-child relation.

A four-bed "rooming-in" unit has been in successful operation at the New Haven Hospital²² for over

a year. Montgomery²³ has used the "rooming-in" system for a number of his private patients in single rooms, with excellent results. In both these groups the mothers were highly selected.

In the private wing of the Boston Lying-in Hospital the "rooming-in" system has been available to mothers scheduled for single rooms for over a year. To date 20 patients have elected this service with but 1 failure. There were nearly 3000 births on the private service during this period, which does not indicate a very great demand. However, more interest in the proposition is evident at present, owing to wide publicity and accelerating interest on the part of the obstetricians. I have no idea how large a proportion of the child-bearing population would elect this system if it were offered to them. Its growth, like that of breast feeding, will depend on prenatal preparation.

On the wards a modification of the "rooming-in" system along the lines of Barnett's²⁴ experience at Los Alamos is planned. It is proposed to keep the babies in the nursery at night but to have the bassinets at the mothers' bedside for the entire day, except for the general visiting hours. So far as possible, the mothers will take complete charge of their babies under expert nursing supervision.

SUMMARY AND CONCLUSIONS

Modern care of the newborn is concerned with attention to factors that may operate before and during birth as well as in the neonatal period. The health and nutrition of the mother from conception on may affect the embryo and fetus and may be responsible for congenital malformations, abortions, stillbirths and premature births. The prenatal period offers the ideal opportunity to prepare the mother psychologically for the nursing and care of her baby.

The major causes of disease in the newborn are anoxic injuries, traumatic injuries, infections, congenital defects and erythroblastosis. Some anoxic injury can be arrested or minimized by improvements in obstetric technic and through the prophylactic use of oxygen. When the anoxic injury is accompanied by generalized edema the administration of fluid is contraindicated. The mortality due to erythroblastosis fetalis has fallen as the result of early delivery in indicated cases with immediate replacement transfusion. If diagnosed promptly, many patients with congenital malformations (such as tracheoesophageal fistulas, absence of the bile ducts, various types of intestinal obstruction and diaphragmatic hernias) now have an excellent chance of being cured by operation. There is good reason to believe that epidemic diarrhea of the newborn can be eliminated through improved nursery technic and the application of simple epidemiologic principles.

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mendations are available to improve the care of these infants in premature nurseries. A major problem remains — the protection of the premature infant from infection during his nursery stay.

While the infant is in the hospital every effort should be made to lay the groundwork for a future sound mother-infant relation. The cultivation of this relation is helped by breast feeding and the adoption of some modification of the "rooming-in" principle.

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Correction On Page 918 of the paper "Diphtheritic Myocarditis" by Drs Boyer and Weinstein, which appeared in the December 9 issue of the *Journal*, the last figure in the column headed "Mortality" in Table 6 should be changed from "78.0" to "89.0". On Page 919 of the same paper, in the second line of the summary, "normal" should be changed to read "abnormal".

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on the right. The trachea was displaced to the right side. At the right base posteriorly there was a relatively homogeneous area of increased density, measuring 8 cm in its greatest dimension. There were several radiolucent zones identified in the upper portion of the density (Fig 2). The right leaf of the diaphragm was elevated. There was no obvious obstruction to any of the major bronchi. Bronchoscopy demonstrated a cherry-red lesion in the posterolateral division of the right lower lobe. The patient bled about 70 cc from the site of the biopsy, which on microscopical examination showed only blood clot.

An operation was performed on the seventh hospital day.

DIFFERENTIAL DIAGNOSIS

DR F DENNETTE ADAMS: The history states that "phrenic crush, solganal-B oleosum and bed rest for five months were employed." I start by confronting this audience with a question and asking for a show of hands. How many know what solganal-B oleosum is?

DR DONALD S KING: I know — since yesterday, that is. (Two other hands were raised.)

DR ADAMS: I first scoured the hospital, and then went to work on the telephone. Finally, while I clung to the receiver, Dr King gave me the answer, but he looked it up. Is that correct, Dr King?

DR KING: Yes.

DR ADAMS: It is a gold preparation, which has been claimed to be very good for arthritis and diseases of the lupus group, except acute lupus, and is of doubtful value in tuberculosis. Dr King tells me that certain groups on the continent are investigating the use of gold in tuberculosis.

DR MALLORY: Is there anything in the record about the percussion note of the lungs and fremitus elsewhere than in the upper portions? (I asked about the percussion note and fremitus because that information might help one decide whether he is dealing with solid tumor, fluid, localized empyema or collapse.)

DR TRACY B MALLORY: The percussion note is checked as being abnormal, but that is not explained or amplified.

DR ADAMS: Fremitus is not mentioned except in the right upper lobe?

DR MALLORY: That is correct.

DR ADAMS: Where the sign is the least dependable. Did the patient run a fever during his hospital stay?

DR MALLORY: The temperature was normal throughout, except for a day following the bronchoscopy, when it was 100°F.

DR ADAMS: The diagnosis must be largely based on the x-ray findings. One cannot make it on history or physical signs alone. The patient was sent

into the hospital because of x-ray findings so we may as well see the films now.

In spite of the normal chest film three years before admission, one wonders if, at the start of the illness, the patient did not have lobar pneumonia that lighted up a latent tuberculosis. If the initial episode was tuberculosis, it is inconceivable that he could have been so acutely ill and recovered so rapidly. One could then further postulate that he developed empyema at that time but absence of evidence of fluid in subsequent x-ray films seems to exclude this possibility. So we must start this problem with his second hemoptysis two years and six months following the first acute illness. Dr Wyman, how far back do your films go?

DR STANLEY M WYMAN: About seven months before entry to this hospital.

DR ADAMS: About the time of the second hemoptysis.

DR WYMAN: These films begin seven months before entry to this hospital and show an infiltrative fibrotic area in the right-upper-lung field, with a small amount of similar infiltration on the left. The trachea is displaced toward the right. The right leaf of the diaphragm is slightly elevated in position, possibly owing to the phrenic crush described. There is an ill defined, round shadow of density in the right-lower-lung field. Four months later there is a suggestion of a large area of rarefaction in the center of the lesion, which may have increased slightly in density at the periphery. The next examination, taken about one month after the second, shows a rather clear-cut, round shadow of considerable density centrally, with indefinite, streaky density extending peripherally.

DR ADAMS: Can we stop here for a moment? This first film shows bilateral apical tuberculosis, with a lesion of some sort in the base, which subsequently showed a cavity. Later, this cavity apparently had filled and became invisible. Is that right, Dr Wyman?

DR WYMAN: The central area is denser on the third film. It may be cavity filled with fluid or something that has grown there.

DR ADAMS: Is the third film to be regarded as a healing process compared to the first film? In other words, is it a tuberculous lesion that is becoming fibrotic?

DR WYMAN: I cannot say that. There is no definite wall about the rarefaction as one usually sees in cavities in tuberculosis. This later density is too sharply defined and homogeneous for the usual tuberculous lesion of this sort. I am not able to picture in my own mind how this thing has come about.

DR ADAMS: That makes two of us.

DR WYMAN: The next examination, done three months after the original, shows about the same picture that we see on the first observation. This changes little, if any, at the next examination four

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

CASE 35021

PRESENTATION OF CASE

A fifty-seven-year-old man was admitted to the hospital after an x-ray study of the chest had revealed a recent infiltration in the right lower lobe



FIGURE 1

The patient was in good health until three years before admission, when chills, fever, dyspnea and hemoptysis of 1 cupful of bright-red sputum appeared. He was given penicillin, and the respiratory symptoms rapidly cleared, but a sense of weakness persisted for several months. X-ray films during the illness showed "scars." The sputum was negative for tuberculosis. Two years before admission he developed a morning cough, productive of a cupful of mucoid sputum, and he became fatigued. Six months later a second hemoptysis

occurred. An x-ray film showed "an apical fibrotic lesion on the right, and a diffuse infiltration at the right base with excavation." The sputum was positive for tubercle bacilli. Phrenic crush, solganal-Bolusum and bed rest for five months were employed. The sputum was positive for two months and then became negative and remained so. X-ray films seven months before admission showed no change in the lesion in the right base (Fig 1). He regained the 25 pounds he had lost prior to hospitalization. He worked for several months but then had several small hemoptyses. X-ray films taken two months before admission showed some spread of the lesion,



FIGURE 2

which was now very pronounced in the right lower lobe. He was given streptomycin for two weeks, but this was discontinued because of nausea. Several chest taps two weeks before admission did not yield any fluid. There had been no recent anorexia, hoarseness, chest pain or weight loss.

Physical examination demonstrated increased breath sounds and tactile fremitus in the right upper posterior chest. Decreased breath sounds were present in the right base. Scattered rales were present in the right axilla. The remainder of the examination demonstrated no abnormalities. The blood pressure was 150 systolic, 85 diastolic.

Laboratory examination showed a normal urine, with a specific gravity of 1.024, a white-cell count of 9700, a hemoglobin of 14.6 gm and a sedimentation rate of 4 mm in 1 hour. Smears of the sputum were negative for acid-fast organisms.

Chest x-ray films showed irregular areas of increased density in both upper lobes, more marked

DR KING You and Dr Davenport agree, but I think I would read tuberculosis in the second film from the left I know the answer, so I am prejudiced

DR WYMAN It looks like it, but the next film does not

DR KING That is true

DR DAVENPORT The cavity is not like tuberculosis

DR WYMAN It does not look like it to me

DR ADAMS But it is a cavity in a patient known to have had tuberculosis That is why I am "hanging my hat" on tuberculosis, but no doubt I have picked the wrong hook

CLINICAL DIAGNOSES

Pulmonary tuberculosis, right upper lobe

Carcinoma, right lower lobe

DR ADAMS'S DIAGNOSIS

Pulmonary tuberculosis, right upper and lower lobes

ANATOMICAL DIAGNOSES

Bronchiogenic carcinoma, right lower lobe

Pulmonary tuberculosis, healed right upper lobe, active right middle and lower lobes

PATHOLOGICAL DISCUSSION

DR MALLORY This is the kind of case to give a clinician whom in the past you have treated very badly

DR ADAMS So you keep on doing the same

DR MALLORY No It is a case on which he cannot be wrong!

This man had both cancer and tuberculosis As you can see from the photograph (Fig 3) the upper lobe is extraordinarily shrunk and consists only of a mass of dilated bronchi embedded in dense scar tissue The present picture is that of localized bronchiectasis In that area I can find neither grossly nor microscopically any evidence of active tuberculosis The middle lobe, in contrast, is considerably enlarged Scattered throughout it are many very small, firm, dense, active tuberculous lesions, but I am afraid they are too small to be visible in the picture The main tumor mass in the lower lobe is a highly differentiated epidermoid carcinoma obviously arising from the lobar bronchus, but all around the tumor, especially toward

the base, is active tuberculosis We do not doubt that he had a cavity, but we did not find any at the time of resection It may well have filled in with tumor

DR ADAMS What was the rationale of operation?

DR LAMAR SOUTTER Dr Sweet operated on him, and our opinion preoperatively was that the

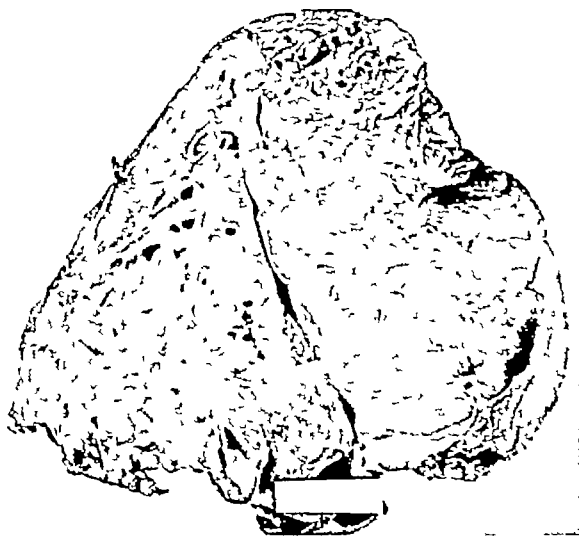


FIGURE 3

patient certainly had tuberculosis We did not believe it was active in the presence of two negative sputum examinations, he had no high temperature, elevated white-cell count and so forth We believed that the most logical explanation for the lesion's increase in size was carcinoma When Dr Sweet opened the chest he thought pneumonectomy was the only possible operation because the amount of tissue left behind would not be valuable Leaving the middle lobe in would be technically difficult and not of any value, and it would be much better to remove the whole lesion

DR WYMAN Was there hemorrhage about the lung adjacent to the tumor?

DR MALLORY Nothing very striking was noted

CASE 35022

PRESENTATION OF CASE

A forty-one-year-old Jewish housewife was admitted to the hospital because of increasing swelling of the abdomen

months later, which is just about three weeks before he entered this hospital. Finally, there is a definite change in the appearance of the lesion, which is now more widely spread, running down to the costophrenic sinus and showing areas of rarefaction in the upper portion.

The bronchi can be fairly well seen. The lateral view shows that the lesion lies in the base of the right lower lobe far posteriorly. I do not know how much the apparent increase in size is due to hemorrhage in and about this lesion.

DR ADAMS: There is no sign of foreign body?

DR WYMAN: Nothing that I can see—no opaque foreign body, at any rate.

DR ADAMS: Are his rib spaces narrowed? Is there any evidence of collapsed lung in the affected area?

DR WYMAN: I do not believe so. One can see the major fissures in the anterior portions of the lungs, suggesting little or no collapse in the lower lobe.

DR ADAMS: It does not look like the picture one sees in coccidiomycosis? Although you say that the cavity wall is thinner than generally seen in tuberculosis, it is not so thin as that which surrounds the cavity of coccidiomycosis?

DR WYMAN: I do not know much about coccidiomycosis.

DR ADAMS: Neither do I, but I have seen some. There is virtually no reaction around the cavity.

Bronchoscopy showed a lesion. But nothing is said about obstruction, and the biopsy demonstrated only blood clot. Following this procedure there was a good deal of bleeding.

I am frank to say that I cannot make a diagnosis. The patient once had active tuberculosis, which was apparently arrested. Then he developed a lesion in the base. At first this must have been regarded as fluid because he was tapped several times. Then he was studied for bronchial obstruction, but no definite evidence of this is recorded. It would be easier if we could presuppose that the high diaphragm was due to collapsed lung, but one cannot assume that it was because the homolateral phrenic nerve had previously been crushed.

Dr King has told me that the effects of phrenic-nerve crush usually endure about six months, in perhaps 15 per cent of cases the nerve may not regenerate at all, provided a thorough crush is done.

DR KING: That is the figure usually quoted.

DR ADAMS: It seems reasonable to assume that the lesion was not collapsed lung secondary to bronchial obstruction or phrenic crush but was in the lung itself. The patient had recently had frequent small hemoptyses. This is not the type of hemoptysis usually seen in tuberculosis. Frequent small hemoptyses bespeak bronchiogenic tumor. We have nothing to substantiate a diagnosis of foreign body. The disease could have been adenoma of the bronchus, it could also have been carcinoma of the bron-

chus. I am relatively certain that the diagnosis was not made prior to operation but that the decision to operate was based on the impression that there was a possibly removable lesion. I can remember in this clinic about a year ago hearing Dr King struggle with one of these cases on which Dr Sweet had operated, my recollection is that both of them said one cannot predict whether a lesion, such as this, is tumor or localized tuberculosis. On the whole, it seems to me most logical to say that this was a tuberculous lesion because we know that the patient had had active tuberculosis. To be sure, no matter which diagnosis one grabs, the answer is always the other. We have a spreading lesion with cavitation in a person known to have had active tuberculosis. We have no definite evidence of bronchial obstruction such as one encounters with adenoma or carcinoma. Cavitation with the two latter is unusual except in the presence of total obstruction. On the other hand the absence of fever and systemic disturbances such as loss of weight and strength is a differential point against active and spreading tuberculosis. Because I have to make a diagnosis, I would put my money, chiefly because the patient has tuberculosis elsewhere, on a tuberculous lesion, but would not be surprised if it turned out to be bronchiogenic tumor.

DR KING: This description of the bronchoscopy worries me. All they say is a "cherry-red lesion." We have no idea about the size, shape or consistency.

DR MALLORY: Did you do the bronchoscopy, Dr Davenport?

DR LOWREY F. DAVENPORT: There was in the posterolateral basal segment of the right lower lobe a small, red lesion, which looked like an adenoma. It was in the bronchus so that it could just be seen faintly, and in grasping the area with the forceps the material was taken out following which there was a gush of blood. The description is not correct. You recall, Dr Mallory, that there were a few cells in the slide, and there was some difference of opinion whether there was enough material to make a diagnosis. It was your opinion that they were tumor cells. I thought from the appearance that probably it was an adenoma, purely because of the bleeding and the suggestive evidence that the bulk of it lay outside the bronchus. Perhaps I was seeing only a small area of infiltrated mucosa with blood clot.

DR KING: Was a study done for tumor cells?

DR MALLORY: Just on the bronchoscopic washings. There were questionable cells mixed in with blood clot from bronchoscopic aspiration.

DR KING: Dr Soutter says that he thinks it was done and was negative.

DR WYMAN: From my point of view I cannot exclude tuberculosis, but I think it is an unusual picture and I had leaned toward tumor, primary bronchiogenic and less likely degenerated adenoma.

safely omit discussion of trauma of the spleen. If the enlargement was not noticed two years before, it must have been a rapidly growing neoplasm. Since it is almost a 75 per cent bet that the findings in this case will be that of metastatic melanotic sarcoma, I think it would be well to review some of the observations about this disease. According to Taylor and Nathanson,¹ this tumor metastasizes early and by way of both the lymphatics and blood stream. In their 265 cases only 25 per cent had five-year cure, 56 per cent of the primary cases had lymph-node metastases, and 74 per cent of the secondary cases had lymph-node disease. Pack,² of New York, finds 50 per cent lymph-node involvement in cases submitted to prophylactic resection. De Cholony,³ in 1941, studied 117 cases from the New York Post-Graduate Hospital and states "melanoma is invariably fatal if not controlled by surgery" and found metastatic disease occurring anywhere from three months to thirteen years after onset, while death occurred from six months to eleven years. His survival rate was more pessimistic—42.3 per cent for the five-year group but only 9.2 per cent for ten-year survival. Before the pessimistic aspect of this becomes too dismal it might be well to mention 2 cases of personal observation that have survived eight to ten years following a lesion on the fourth toe and another, in a doctor's wife, picked up early on the great toe in which the patient remained well following radical excision of that tumor and groin dissection. It is possible that the patient in the case under discussion had a bizarre finding such as an ovarian cyst on a long pedicle lying in the left upper quadrant. The most likely reason for the operation must have been an attack on the spleen itself or merely exploration for diagnostic purposes.

Unless a totally different neoplasm was discovered at this operation, I would expect the findings to be those of extensive metastatic melanotic sarcoma involving the retroperitoneal area and possibly other abdominal organs. Dr Smithwick had

a case in this hospital recently with a small primary lesion on the right upper arm, autopsy two years later showing the disease involving the lungs, the liver, the kidneys and the small intestine. I do not know of any cases that include splenic involvement, nor did I find any in the literature, but I understand that there is one such case in a male patient in this institution.

CLINICAL DIAGNOSIS

Ovarian cyst?

DR SIMMONS'S DIAGNOSIS

Metastatic melanotic sarcoma

ANATOMICAL DIAGNOSES

Metastatic melanotic sarcoma

PATHOLOGICAL DISCUSSION

DR TRACY B. MALLORY: It was believed on the wards that there was sufficient possibility that this large abdominal mass was something other than metastatic melanoma to warrant exploratory laparotomy. The patient was operated on with a preoperative diagnosis of "question of ovarian cyst." As soon as the abdomen was opened considerable quantities of serosanguineous fluid escaped through the incision.

As the abdomen was explored great masses of metastatic tumor were found. They appeared to be both retroperitoneal and intraperitoneal, and tumor was present in the omentum, the mesentery and in the liver. Biopsies from several areas all showed malignant melanoma.

REFERENCES

- 1 Taylor G W and Nathanson I T. *Lymph-Node Metastases: Incidence and Surgical Treatment in Neoplastic Disease*. 493 pp. New York: Oxford University Press, 1942. Pp 115-126.
- 2 *Treatment of Cancer and Allied Disease*. Edited by G T Pack and E M Livingston. 3 vol. 2593 pp. New York: Paul B Hoeber Inc. 1940.
- 3 DeCholony T. Malignant melanoma: clinical study of 117 cases. *Ann. Surg.* 113:392-410 1941.

Three months before admission the patient noted some discomfort and pain in the left upper quadrant, which occasionally radiated across the abdomen to the right midabdomen. One month before admission she noted an increasing swelling of the abdomen, with a mass in the left side. The mass became acutely tender for a week, and then the tenderness subsided. She gave a past history of having had an appendectomy at the age of twenty-one and an excision of a mole from the abdomen at thirty-one. Six years before entry she had noted some epigastric pain. A gastrointestinal series at that time was reported to be negative. Two years before the present admission she had a pigmented lesion on the lateral aspect of the right ankle excised, and the defect grafted. The lesion measured 1.5 by 3.5 cm in diameter, and the pathological diagnosis was malignant melanoma. There were two questionably enlarged lymph nodes in the right groin, and four weeks later a right radical groin dissection was done. Pathological examination showed no evidence of cancer. At this time there was no evidence of intra-abdominal disease on physical examination. Pelvic examination was not done.

On physical examination the abdomen was protuberant, and there was a huge, fixed, round mass in the region of the spleen. The uterus contained several fibroids. There was no palpable lymphadenopathy. The blood pressure was 130 systolic, 80 diastolic.

Laboratory examination demonstrated a red-cell count of 3,370,000, with a hemoglobin of 9.2 gm, and a white-cell count of 10,400, with a normal differential. The urine was normal. Vaginal smear was negative for tumor cells.

X-ray examination of the abdomen, including a pyelogram, suggested a large, ill defined, intraperitoneal mass in the left midabdomen. The stomach was displaced upward and to the right, as were several loops of small bowel. There was no definite calcification in the mass.

An operation was performed.

DIFFERENTIAL DIAGNOSIS

DR FRED A. SIMMONS. It would be helpful to know the duration preoperatively of this pigmented lesion. The lesion is described as measuring 1.5 by 3.5 cm in diameter. It occurred to me in reviewing this case that it would often be valuable in these

exercises to have preoperative and postoperative photographs in cases with superficial lesions. These would help characterize the lesion and also aid in evaluating the extent of the operation. This lesion was approximately average in size for a malignant melanoma, since the mean is 3 cm, according to Taylor and Nathanson.¹

A right radical groin dissection was done. It would be valuable to know whether this dissection included removal of the lymph nodes up to the bifurcation of the external and internal iliac vessels. The pathological examination of the nodes showed no evidence of metastasis. A careful search of the current literature and two texts on the subject of cancer failed to emphasize a point that should be brought out here. The disease and other malignant neoplasms often skip the normal distribution into the adjacent nodes, and the disease has often progressed into the abdominal or thoracic cavity while the adjacent lymph nodes are reported to be normal.

It would be of interest to know if the physical examination was done by a medical man or a surgeon, for the medical man often finds spleens that the surgeon does not report. The next sentence implies that the physical examination must have been medical, for it says "no pelvic examination was done." The protuberance may have been due to ascites, but there is no further mention of this. A vaginal smear was negative for tumor cells. I think we may assume that the patient entered this time on the Gynecologic Service.

X-ray examination of the abdomen included a pyelogram. It would be interesting to know if the roentgenologist was willing to express an opinion whether the large mass was intraperitoneal or retroperitoneal. It would be more definitive if "large" could be modified by some measurement. It would be a great help here to have had a barium enema. The absence of calcification would tend to rule out dermoid cyst.

According to previous exercises in this room the negative history of gastrointestinal, genitourinary, gynecologic and neuromuscular systems implies that such history was negative and, therefore, not reported. This leaves us with a lesion that, for lack of any other involvement, must have been retroperitoneal, adrenal or possibly splenic. For the sake of brevity I will omit consideration of the usual medical causes for splenomegaly and can probably

safely omit discussion of trauma of the spleen. If the enlargement was not noticed two years before, it must have been a rapidly growing neoplasm. Since it is almost a 75 per cent bet that the findings in this case will be that of metastatic melanotic sarcoma, I think it would be well to review some of the observations about this disease. According to Taylor and Nathanson,¹ this tumor metastasizes early and by way of both the lymphatics and blood stream. In their 265 cases only 25 per cent had five-year cure, 56 per cent of the primary cases had lymph-node metastases, and 74 per cent of the secondary cases had lymph-node disease. Pack,² of New York, finds 50 per cent lymph-node involvement in cases submitted to prophylactic resection. De Cholony,³ in 1941, studied 117 cases from the New York Post-Graduate Hospital, and states "melanoma is invariably fatal if not controlled by surgery" and found metastatic disease occurring anywhere from three months to thirteen years after onset, while death occurred from six months to eleven years. His survival rate was more pessimistic—42.3 per cent for the five-year group but only 9.2 per cent for ten-year survival. Before the pessimistic aspect of this becomes too dismal it might be well to mention 2 cases of personal observation that have survived eight to ten years following a lesion on the fourth toe and another, in a doctor's wife, picked up early on the great toe in which the patient remained well following radical excision of that tumor and groin dissection. It is possible that the patient in the case under discussion had a bizarre finding such as an ovarian cyst on a long pedicle lying in the left upper quadrant. The most likely reason for the operation must have been an attack on the spleen itself or merely exploration for diagnostic purposes.

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ALPHA AND OMEGA

IN INFANCY and crabbled age an immortality and a fate are presented to mankind. The former, because full of promise, is easier to contemplate and also easier to serve, as witness the readiness with which funds, public and private, are obtained for infant and child welfare, and the increasing scope of effective medical care in this field. As infant mortality has decreased, however, and an ever larger proportion of survivors, healthy to start with, is kept in health, the inevitability of old age increases, but not necessarily its miseries.

In this issue of the *Journal* Clifford recounts the achievements of preventive medicine in the life of the embryo and fetus as well as in the newborn

child. The old wives' tales of a child being "marked" by an experience of the pregnant mother have here modern scientific support. Infections, attempted abortions and poor diet may mark an unborn child with a congenital malformation and may predispose him to the hazards of prematurity or to death by miscarriage or stillbirth. Also, the infant may receive favorable marks from the moment of conception by appropriate medical supervision. In the prenatal period not only are the ill effects of infection, trauma, incompatible blood and inadequate diet prevented but also the mother in a more positive sense may be prepared psychologically for the nursing and care of her child. In this particular the "rooming in" system whereby mother and baby may remain together returns them to the relations of the home and yet affords the scientific protections of the modern hospital.

If babies do not arrive naturally and full-fledged, trailing clouds of glory, but require hard, precise supervision for nine months after the time of conception, neither is the traditional misery of old age as inevitable as supposed. For eight years a geriatric clinic in Boston has been stating the medical problems of old age, asking in what ways health and disease differ in the evening of life and what one does about them. Happily, Monroe, also in this issue of the *Journal*, has made available the benefit of his experience. It appears that, in the second childhood as in the first, nutrition is extremely important, that no play makes these old Jacks the dull boys that they so often are, and that unoccupied old minds like their young counterparts get into slothful or other bad habits.

The extension of individual preventive medicine into the fetal period and the support it gives to certain of Grandma's observations may be viewed with great satisfaction. It is a source of gratification that in lying-in hospitals mother love at last is asserting itself over the nursing supervisor's efficiency and the pediatrician's feeding schedule. It is not so gratifying to realize that one of the few manifestations of filial piety in modern life is the development of geriatrics as a medical specialty, pleasing as it is to contemplate the renewed interest in this phase of medical care.

ARE WAR YEARS GOOD YEARS?

SHORTLY before his death, the late John Winant asked an audience "Are you doing as much for peace as you did for this country and civilization in the days of war?" It is a question well worth pondering. It leads one eventually to consider the incentives for working actively toward peace. Bizarre as it may seem, such incentives do not appear to be very clear in the minds of the American people. To a European whose home was destroyed, whose business was disrupted and who may have been starved, incarcerated, or tortured during the recent war, peace is obviously better than war if only for purely materialistic reasons. To the American who suffered no such privations the evidence that peace is preferable to war may be far less vivid. In fact, according to a recent analysis,* most statistical indexes indicate that war years are more prosperous than peace years. Industrial production, factory employment, hourly earnings and the gross national product all began to rise about 1937 and continued to rise steadily during the war years. They seem to have been influenced little, if any, by the war. The indexes ordinarily used to measure business cycles (bank clearings outside New York City, freight-car tonnage, industrial production, business failures and wholesale commodity prices) show that the periods covered by World War I and II have all the earmarks of prosperity. Public assistance (relief) and business failures declined precipitately from 1940 onward. Business profits, like production, "were greater than usual in the war year 1917, and again the years of the second world war, 1942-45." Indexes, indicative of social conditions, such as marriages, births, deaths and divorces, seem to have been very little affected by the war and certainly were not adversely affected. The statisticians were able to produce very little evidence that war is economically undesirable, although their data do show that taxes and the public debt went up while public works declined during the war years. Nor does their evidence touch on the obvious fact that most of our enormous wartime production was not available or suitable for civilian use.

*Osborn, W., and Adams J. "Are our wars good times?" *Scient. Monthly*, 67:23-33, 1948.

In spite of the incompleteness of purely financial evaluations of the effects of war, such reports unquestionably exert an insidious influence on many people. Confronted with such evidence and recalling his high pay and full employment during wartime what is the American worker to conclude? The businessman also, viewing his increased profits and the seller's market, can hardly regard war as altogether bad. It is perhaps too much to expect these groups to look beyond such statistics and their own wartime business experience to see the unmeasured and perhaps incalculable damage wrought by war on a participating population, no matter how far removed from the actual fighting. The authors of the treatise in question candidly state "The positive association of good times in the United States during the war probably has a bearing upon our willingness to engage in another war." One might put it even more strongly.

Physicians, especially those who served in the armed forces, are in a better position to penetrate the veil of material prosperity and visualize the malignant effects of war. Like the public debt, the disruption of scientific education at all levels and, to some extent, of scientific research will weigh heavily in the future. The vast wastage, not only of materials but especially of scientific talents and skills, was painfully apparent, unavoidable though such wastage may have been. The tangible and intangible effects of wartime fear and insecurity should be apparent to the physician, of all people. These and many more features, whether the statistician's indexes uncover them or not, must ultimately be taken into account by everyone, doctor or layman.

Finally, as the authors point out, this country may not escape vast internal damage if it engages in another war. Whether war can be avoided is problematic. In any case, the country should not enter on any such project without full and sober consideration of the evils of war that business and financial statistics do not reveal. The physician has first-hand knowledge of many of these relatively occult features, and if he does his part to make the layman aware of them, and to keep them crystal clear in his own mind, he can answer Mr. Winant's question with a resounding yes!

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MASSACHUSETTS MEDICAL SOCIETY

DEATHS

CARTER — Arthur C Carter, M D of South Dartmouth, died on November 26. He was in his forty-ninth year.

Dr Carter received his degree from Tufts College Medical School in 1936. He was formerly superintendent of Sassaquin Sanatorium in New Bedford.

His widow, his father and two daughters survive.

CURRIER — W Eugene Currier, M D, of Leominster died on November 23, 1948. He was in his seventy-eighth year.

Dr Currier received his degree from Harvard Medical School in 1898. He was formerly school physician in Leominster and a member of the staff of Leominster Hospital.

His widow and two nephews survive.

GEORGE — Arrial W George, M D, of Wellesley Hills, died on December 25. He was in his sixty-seventh year.

Dr George received his degree from Tufts College Medical School in 1906. He was radiologist at Brooks Hospital, Brookline, Glover Memorial Hospital, Needham, and Massachusetts Institute of Technology. He was a former chancellor of the American College of Radiologists, a member of the New England Roentgen Ray Society, American Roentgen Ray Society and Radiological Society of North America, Inc., and a fellow of the American Medical Association.

His widow, two sons and a sister survive.

OVERLANDER — Charles L Overlander, M D, of Boston died on December 16. He was in his seventy-sixth year.

Dr Overlander received his degree from Harvard Medical School in 1905. He was a member of the American College of Physicians and a fellow of the American Medical Association and was director of the Pathological Laboratory at Brooks Hospital, Brookline.

His widow and a brother survive.

QUIST — F Julius Quist, M D, of Worcester, died on December 20. He was in his seventy-fourth year.

Dr Quist received his degree from Rush Medical College in 1905. He was a fellow of the American Medical Association.

His widow, a brother and a nephew survive.

SILVERSTEIN — Maurice L Silverstein, of Boston, died in the military service on February 16, 1946. He was in his forty-eighth year.

Dr Silverstein received his degree from Boston University School of Medicine in 1923.

MISCELLANY

AWARD TO NATIONAL INSTITUTES OF HEALTH

Dr Rollo E Dyer, director of the National Institutes of Health of the United States Public Health Service, received on December 7, 1948, in behalf of his organization the 1948 Award of Distinction from the American Pharmaceutical Manufacturers' Association in recognition of the Institutes' "great contributions to public health through fundamental medical research for the profound benefit of mankind." Presentation of the award was made by Dr Ernest E. Irons, president-elect of the American Medical Association.

The National Institutes of Health include the National Cancer Institute, the National Heart Institute, the National Institute of Dental Research, the National Institute of Mental Health, the Institute of Experimental Biology and the Institute of Microbiology.

CANCER RESEARCH UNIT AT COLUMBIA

Columbia University has announced its plans for a \$2,000,000 cancer research unit to be constructed on top of the present Vanderbilt Clinic at the Columbia-Presbyterian Medical Center. Half the construction cost will be provided by the National Advisory Cancer Council and half by Columbia University.

AMERICAN COUNCIL ON RHEUMATIC FEVER OF AMERICAN HEART ASSOCIATION

Dr Ruston McIntosh, director of the Pediatric Service, Presbyterian Hospital, and Carpenter Professor of Pediatrics, Columbia University College of Physicians and Surgeons, has been elected 1949 chairman of the American Council on Rheumatic Fever of the American Heart Association.

Mr Lawrence Linch of Chicago was elected vice-chairman.

Newly elected members of the Council's Executive Committee include, in addition to Dr McIntosh, Mr A W Robertson (*ex officio*), chairman of the Board of the American Heart Association, Pittsburgh, Dr Hugh McCulloch, St. Louis, Dr Walter Bauer, Boston, Dr David D Rutstein, Boston, Dr Edward Harmon, Valhalla, New York, Dr M J Shapiro, Minneapolis, Dr T Duckett Jones, New York City, Dr Homer F Swift, New York City, and Dr George M Wheatley, New York City.

QUARTER, QUARTER, WHO HAS THE QUARTER?

S 1320 [Wagner-Murray-Dingell Bill], Section 204

(a) Every individual shall be eligible for benefits under this title throughout any benefit year if —

(1) he has received (or, in the case of incomes from self-employment, has accrued) —

(A) not less than \$150 in wages during the first four of the last six calendar quarters preceding the beginning of the benefit year, or

(B) not less than \$50 in wages in each of six calendar quarters during the first twelve of the last fourteen calendar quarters preceding the beginning of the benefit year (not counting as one of such fourteen calendar quarters any quarter in any part of which the individual was under a total disability which continued for six months or more),

(2) he is entitled, for the first month in the benefit year, to a benefit under title II of the Social Security Act, as amended, or to an annuity under the Civil Service Retirement Act, as amended, or

(3) he is on the first day of the benefit year a dependent of an individual who is eligible under paragraph (1) or paragraph (2).

OUTPATIENT TREATMENT OF VETERANS

Nearly 2,000,000 veterans received outpatient treatment from the Veterans Administration during the fiscal year ending June 30, 1948. The treatments were given at regional offices, hospitals and clinics, and by private physicians co-operating with the Veterans Administration in providing home-town care for veterans with service-connected disabilities.

Treatments averaged 3 per veteran, or a total of 5,223,680. Patients treated numbered 1,937,842.

Private physicians treated 761,185 veterans, or about 40 per cent of the total. The physicians were paid \$11,437,870 for 2,735,450 treatments, or an average of \$4.18 per treatment or \$15.03 per veteran undergoing medical care.

Veterans Administration staff doctors during the year treated 1,176,657 individual veterans, providing a total of 2,498,230 treatments.

CORRESPONDENCE

HISTOPLASMIN REACTIONS

To the Editor The publications concerning histoplasmosis have proved the importance of this interesting infection. Up to this time we at the Wrentham State School have had no possibility of publishing our experiences.

In the fall of 1946, we were supplied with a small amount of extract by Dr Herman Vollmer. In our first series 0.1 cc of a solution of 1:1000 was administered intracutaneously to 200 patients, 2 of whom showed, on the third day, a mild local reaction, which disappeared on the fourth day. One of them had a positive Pirquet reaction. In the other, a seventeen-year-old boy, the Pirquet reaction was negative, and x-ray examination showed a peculiar appearance of the lungs, resembling tuberculosis.

SURVEY OF MEDICAL EDUCATION

BEGINNING with the new year, the Council on Medical Education and Hospitals of the American Medical Association and the Association of American Medical Colleges have put on foot a three-year joint survey of medical education in the United States. To further this project a committee of seven has been appointed, composed of leaders in medical education, and Dr John E. Deitrick, of New York, has been selected as the full-time director of the survey. Dr Deitrick, a graduate of Johns Hopkins University School of Medicine, is associate professor of medicine at the Cornell University Medical College, and medical director and director of post-graduate instruction of the Second Medical Division, Bellevue Hospital.

The objects of the study, as stated by the committee, are to evaluate the present programs and determine the future responsibilities of medical education in its broadest aspects, in order to improve medical education better to meet the needs of the American people for the prevention of disease, the expedition of convalescence and the maintenance of health, to assess the degree to which medical schools are meeting the needs of the country for physicians, to promote the advancement of knowledge in the field of medical science, and to inform the public concerning the nature, content, and purposes of medical education.

The present survey is the third that has been made in forty years. The first resulted in the Flexner Report, published in 1910 by the Carnegie Foundation for the Advancement of Teaching, the second resulted in the Weiskotten Report, published ten years ago.

This timely survey will undoubtedly consider various factors that concern the future of medical education—the problem of preparedness for national emergencies, the social aspects of medicine in all their ramifications, the place that medical practice will occupy, and the sources of the funds with which the costs will be defrayed.

The world has become a social laboratory in which medicine must play its part in interpreting the reactions

HISTOPLASMOSIS IN MASSACHUSETTS*

PREVIOUSLY in these columns* mention was made of the possible significance of histoplasmosis as the cause of the unexplained cases of disseminated areas of calcification visible in x-ray films of the lungs in nonreactors to tuberculin who give positive skin reactions to histoplasmin. Attention was called to the recent surveys, particularly those carried out in Kansas City, Missouri, and in Tennessee, which uncovered a large number of such persons. Studies among nurses also revealed a high incidence in the eastern central area of the United States, and the frequency of their occurrence diminished progressively in proportion to the distance from this area. It was noted at that time that histoplasmosis was not known to occur in New England but that it had been reported from areas as close as New York and Washington, D. C.

In a letter from Mautner, which appears elsewhere in this issue of the *Journal*, evidence is presented suggesting that infections with histoplasma might indeed occur in an unrecognized form in Massachusetts. The evidence, to be sure, is far from conclusive. It is based upon the demonstration of local reactions in the skin of patients at the Wrentham State School following intracutaneous injection of histoplasmin. Of 200 patients tested with 0.1 cc of a 1:1000 dilution, only 2 showed mild reactions that were delayed, and injection of a larger amount—namely, 0.1 cc of a 1:100 dilution—yielded 19 reactors among 100 patients, and the reactions were more intense and occurred earlier. All but one of the histoplasmin reactors showed positive tuberculin tests. The negative tuberculin reactor who was tested with the smaller amount, and 4 of those who reacted to the larger amounts of the histoplasmin showed some areas of pulmonary calcification in roentgenograms of the chest. Mautner's findings, though inadequately controlled and not proving conclusively that his reactors had histoplasmosis, suggest that this infection should be considered in the differential diagnosis of patients with diffuse pulmonary lesions in which other more likely diagnoses can be ruled out.

*Editorial. Nontuberculous pulmonary calcification. *New Eng J Med* 237:171, 1947.

The author, in this short monograph, presents 47 cases of chronic disease relieved by drainage of the nasal sinuses. The diagnosis of the condition was made largely through an intensive study of the fields of vision. A short bibliography and a list of cases conclude the text. There is a good index. The publishing is excellent. The price is reasonable. The volume should prove interesting to ophthalmologists and rhinologists.

Modern Trends in Dermatology Edited by R M B MacKenna, M A, M D (Camb), F R C P (Lond), physician-in-charge, dermatological department, and lecturer in dermatology, St Bartholomew's Hospital, London physician to St. John's Hospital for Diseases of the Skin, London honorary consultant in dermatology to the British Army and examiner in dermatology, Royal Army Medical College. 8° cloth 432 pp, with 32 illustrations. New York: Paul B Hoeber Incorporated, 1948. \$5.50.

This composite work of twenty-three dermatologists presents the modern conception of dermatology in varying aspects. The first chapter constitutes a short history of dermatology, followed by special chapters, including psychologic aspects, problems in tropical and subtropical areas, the prevention of cutaneous diseases (excluding industrial diseases) and the rehabilitation of dermatologic patients. The question of rehabilitation has received needed attention only recently. Bibliographies are appended to the chapters. The type and printing are good, but the use of a coated paper is not justified by the few noncolored illustrations. The volume is recommended for all medical libraries.

The Scientific Paper. How to prepare it, how to write it. A handbook for students and research workers in all branches of science. By Sam F Trelease, Columbia University. 12° cloth, 152 pp, with 8 illustrations, 7 tables. Baltimore: The Williams and Wilkins Company, 1947. \$2.00.

This is a new edition of the author's *Preparation of Scientific and Technical Papers* published in 1936. The text has been thoroughly revised and largely rewritten. The manual is intended for students and research workers but should prove valuable to physicians who are called on to write papers for publication. It covers the whole field from outlining and writing the paper to proofreading. A good index concludes the volume. It is recommended for all medical libraries.

Medical Hypnosis. Vol I. The Principles of Hypnototherapy. Vol II. The Practice of Hypnototherapy. 8°, cloth, Vol I 449 pp, Vol II, 513 pp. New York: Grune and Stratton, 1948. Vol I, \$5.50, Vol II, \$6.50.

This comprehensive treatise covers the whole field of hypnototherapy. The second volume is devoted to discussions of hypnosis in the removal of symptoms, in psychobiologic therapy, and in psychoanalytic therapy. The work is well published. The set is recommended for large medical libraries and to psychiatrists.

The Skull, Sinuses and Mastoids. A handbook of roentgen diagnosis. By Barton R Young, M D, professor of radiology, Temple University Medical School. 8°, cloth, 328 pp, with 141 plates. Chicago: The Year Book Publishers, Incorporated, 1948. \$6.50.

This volume is one of a series of handbooks on x-ray diagnosis projected by the publishers. The text is divided into three parts: the skull, the nasal sinuses and the mastoids. The text comprises descriptions of various conditions, each of which is illustrated with a radiographic plate. The type, printing and plate work are good. A bibliography and a good index conclude the volume. The seemingly large price is justified by the large number of plates. This volume and its companions should be in all medical libraries and in the libraries of radiologists.

The Diabetic's Handbook. How to work with your doctor. Treatment by diet and insulin. By Anthony M Sindoni, Jr, M D, chief, Department of Metabolism, Philadelphia General and St. Joseph hospitals, chairman, Advisory Committee on Dia-

betes to director of Department of Public Health, Philadelphia and chief diseases of metabolism, St. Francis Hospital, Wilmington, Delaware. With an introduction by Rufus S Reeves, M D, director, Department of Public Health, Philadelphia. With a foreword by Charles C Wolferth, M D, professor of medicine, School of Medicine, and administrator of the Robinette Foundation for Research in Cardiovascular Disease, University of Pennsylvania, director for cardiology, Professional Services Division, Veterans Administration and consultant cardiologist to the Jewish Hospital. 8° cloth, 194 pp. New York: The Ronald Press Company, 1948. \$3.00.

This manual for the diabetic patient is the joint work of seven physicians. The material is well written and well organized. The section on foods, documented with a number of tables, comprises sixty-three pages. A good index concludes the volume. The book is well published and should prove useful to patients and their families.

Intracranial Tumors. By Percival Bailey, M D, professor of neurology and neurological surgery, University of Illinois. 8° cloth, 471 pp, with 155 illustrations and 16 plates. Second edition. Springfield, Illinois: Charles C Thomas, 1948. \$10.50.

This second edition of an authoritative treatise has been revised to include the recent advances in knowledge, and a brief atlas of roentgenographic photographs has been added as an appendix. A comprehensive bibliography concludes the text. There is a good index. The volume is well printed with good type on lightweight, nonglare paper. It is recommended for all medical libraries.

NOTICES

ANNOUNCEMENT

Dr Arthur L Hanrahan announces the removal of his office from 45 Bay State Road to 270 Commonwealth Avenue, Boston, for the practice of surgery.

GEORGE F BAKER CLINIC

The Committee on Diabetes, appointed by action of the Massachusetts Medical Society, has suggested that clinical exercises in diabetes be offered without charge in various hospitals for physicians. To this end the George F Baker Clinic at the New England Deaconess Hospital offers exercises on Monday and Friday of each week. The schedules are as follows:

Monday, 8:00-9:00 a.m., Second Floor, New England Deaconess Hospital. Case Presentations in Diabetes and Surgery of the Extremities.

Friday, 8:00-8:15 a.m., Second Floor, New England Deaconess Hospital. X-Ray Pathology in Diabetes.

8:15-9:00 a.m. Classroom, George F Baker Building. Case Problems in Treatment of Diabetes and Complications. Pregnancies, acidosis, insulin resistance and so forth.

9:00-10:30 a.m. Medical Rounds for Visiting Physicians. 9:00-10:30 a.m. Instruction in Diet and Urine Testing (for Office Nurses, Technicians or Secretaries Sent by Physicians).

10:30-11:15 a.m. Class Teaching in Diabetes (Physicians, Office Assistants and Nurses are welcome).

SOUTH END MEDICAL CLUB

A regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, January 18, at 12 noon. Dr Lawrence C Kingsland, Jr, will speak on the subject "Respiratory Infections in Children." The lecture will be illustrated with lantern slides. All physicians are cordially invited. Luncheon will be served after the lecture at a cost of 60 cents. Reservations should be made for the luncheon.

In January, 1947, we were supplied with a stronger extract of 1 100, 01 cc of this solution was administered to 100 patients. Nineteen showed a local reaction on the following day. In 9 of them the reaction was quite strong, but only 6 were positive on the next day. All 19 patients showed a positive tuberculin reaction. X-ray films of 4 showed calcification of the lung, which could easily have been Ghon nuclei or calcified lymph nodes. One film even looked somewhat peculiar for tuberculosis.

The examinations have not been continued, since it was difficult to obtain the extract at that time. Nevertheless, it seems that isolated infection with histoplasma, without severe sequel, occurs in Massachusetts.

The patients examined were in the care of the Wrentham State School, and the last series of 100 were in a building where the older women live.

HANS MAUTNER, M D

Wrentham State School

HOW TO MAKE FRIENDS AND INFLUENCE PEOPLE

To the Editor The following safe advice, presented to the meeting of secretaries and editors at St. Louis, speaks for itself.

FRISCO DOCTOR PRESENTS HIS OWN PROGRAM In this day and age when everybody is talking himself hoarse about medical plans and programs, Dr. Anthony B. Diepenbrock, of San Francisco, comes up with his own 13-point health program which, he says, "might be interesting to our colleagues."

1 Continue to sit on your fat derriere and do nothing.

2 Be apathetic and, like 5,000,000 registered Republican voters who failed to vote, do not bother to make your opinion known. If you think, as they did, that your opinion or your vote is not worth anything, the opposition will agree with you and act accordingly, as they have.

3 Write an occasional letter to your congressman, tell him off, and then explain proudly to the intern in the surgical dressing rooms how smart you are and what a stinker your congressman is.

4 Tell everybody you see that the gag is up, and we might as well prepare for the inevitable.

5 Moan and groan and issue explosive and unprintable epithets.

6 Refer to your medical leadership as a group of impotent, ineffective and bumbling ignoramuses.

7 Make speeches before sympathetic lay audiences, and convert those who already believe in free enterprise.

8 Don't bother to tell your county society heads, your state society heads, or your national association heads what you want them to do. Expect them to find a way for you without your guidance.

9 Scream about high medical society dues and forget that our friends in the trades unions demand many times what we pay. In other words, make the situation as difficult as possible, then grumble about it.

10 Oppose any program developed by the majority of your colleagues because it demonstrates your superior wit and your general greatness.

11 Remain superbly and learnedly dignified when Joe Doakes asks why you oppose state medicine. Brush him aside with any insult you can think of. Joe will like you for that.

12 Don't bother to use the selling methods which actually bring messages before the public. Continue to depend on occasional radio feature programs. Billboard advertising, newspaper advertising, national magazine advertising, radio advertising and above all, continuous and daily radio spot programs over national hookups and all such like are too commercial, too troublesome, too expensive and too undignified don't use them.

13 Above all, disregard the "little guy" — the one with a vote. Tell him nothing, push him around. He doesn't know anything anyhow.

H. QUIMBY GALLUPE, M D

8 Fenway, Boston

SOUTH CAROLINA LEADS

To the Editor In the December 2 issue of the *Journal*, I read with interest your editorial on the Massachusetts Medical Benevolent Society, "the oldest of its kind in continuous existence in the United States," calling attention to its ninety years of useful and beneficent activities. I now respectfully direct your attention to Charleston, America's Most Historical City, where, on January 12, 1949, The Society for the Relief of the Families of Deceased and Disabled Indigent Members of the Medical Profession of the State of South Carolina, today referred to as the Widows and Orphans Society, is having its Centennial Banquet. In its early days the treasurer's books carry the name of the Medical Benevolent Society. The Society was organized in 1848 and was incorporated on December 19, 1849. Annually, it has contributed to its beneficiaries. One reason for its continued growth is a wise provision in the Constitution to the effect that a fourth of the annual income must be reinvested. According to its Constitution "any person of good moral character" may be a member. "The members of the Society shall annually assemble and dine or sup together, in the City of Charleston, on the second (2nd) Wednesday of January in every year." The Stewards are to provide and the Treasurer is to pay for the supper.

LEON BAYOV, JR., M D

1041½ Rutledge Ave.,
Charleston 16, S C

NOTE: Apologies and congratulations to the medical fraternity of South Carolina — Ed

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

War, Politics, and Insanity. By C. S. Bluemel, M A, M D, M R C S (Eng). 8°, cloth, 121 pp. Denver: The World Press, Incorporated, 1948. \$2.00.

The author in this monograph discusses the psychological qualities of political leadership and the disorders of personality with which aggressive leadership is commonly associated.

Modern Clinical Psychiatry. By Arthur P. Noves, M D, superintendent, Norristown State Hospital, Norristown, Pennsylvania. Third edition. 8°, cloth, 525 pp. Philadelphia: W. B. Saunders Company, 1948. \$6.00.

This third edition of a textbook, first published in 1934 and revised in 1939, has been largely rewritten, and three chapters have been added on psychotherapy, shock and other physical therapies and child psychiatry. The material on the psychoneuroses has been amplified, and that on psychosomatics has been extended. The book is based on lectures originally presented to senior medical students. The material is well organized and well written, and the publishing is excellent.

Subacute Bacterial Endocarditis. By Emanuel Libman, M D, and Charles K. Friedberg, M D, adjunct physician, Mt. Sinai Hospital, New York City. Edited by Henry A. Christian, A M, M D, LL D, Sc D (Hon.), M A C P, Hon. F R C P (Can), D S M (Am Med Assoc). 8°, cloth, 113 pp., with 19 illustrations. New York: Oxford University Press, 1948. \$3.50. Reprinted from *Oxford Loose-Leaf Medicine* with the same pagination.

This monograph is a reprint from the *Oxford Loose-Leaf Medicine*, published in book form, making it available to interested physicians who do not have the system. The text reflects the latest information on the subject. A large bibliography concludes the text. The publishing is well done.

Chronic Ill-Health, Relieved by Drainage of the Para-Nasal Sinuses. By Rosa Ford, M B (Lond), D O (Oxon). 12°, cloth, 104 pp., with 13 illustrations. London: Henry Kimpton, 1948. 6/6 net.

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GASTROJEJUNOCOLIC FISTULA*

Review of Nine Cases, with Use of Vagus Resection as Part of the Operative Procedure in One

HENRY H. FAXON, M.D.,[†] AND WILLIAM G. SCHOCH, JR., M.D.[‡]

BOSTON AND FRAMINGHAM, MASSACHUSETTS

GASTROJEJUNOCOLIC fistula following gastrojejunostomy has long been considered one of the most serious complications of gastric surgery. Historically, the initial reports on the evolution and correction of the condition include the description by Wolfer of the first gastroenterostomy in 1881, the recognition by Braun of a gastrojejunal ulcer eight years later, the finding by Czerney¹ of a fistula into the colon at the site of a previous gastroenterostomy in 1903, and the surgical intervention for the correction of the condition by de Herezel² in 1905.

The surgical problem is solved by removal of the fistula, restoration of bowel continuity and correction of the ulcer diathesis. Because vagus resection has not been reported as the method of dealing with this last factor, a case from the Cushing Veterans Administration Hospital is cited in which it was successfully employed after restoration of the continuity of the intestinal tract, and the data on 8 other cases of gastrojejunocolic fistula from the Massachusetts General Hospital are added.

INCIDENCE

In 1941 Bornstein³ reviewed the literature and found only 322 cases of gastrojejunocolic fistula, thus suggesting that the experience of any one surgeon in treating the condition must, of necessity, be limited. In the past forty years there have been but 18 such patients admitted to the Massachusetts General Hospital,^{4, 5} and no case has been encountered since 1941. The decreasing incidence can be explained chiefly by the steadily growing enthusiasm

for gastric resection rather than gastroenterostomy in the treatment of duodenal ulcer. The extent to which this shift in the surgical approach has taken place is illustrated by a threefold increase in resections for duodenal ulcer at the Massachusetts General Hospital during recent years, as contrasted with the near disappearance of the operation of gastrojejunostomy alone (Fig. 1). Vagus resection has also been adopted during the last four years as another method of surgical treatment of an appreciable number of patients.

It is far from true, however, that gastrojejunocolic fistula can now be considered an obsolete entity. Because of the long interval between gastroenterostomy for ulcer and the occurrence of fistula (Table 1) there is bound to be a continuing residue of such fistulas for an appreciable period. Furthermore, some surgeons still perform gastroenterostomies without resection for duodenal ulcer, thus establishing the potential origin of a gastrojejunocolic fistula. In addition, partial gastric resections that inadequately control the ulcer diathesis may produce marginal ulcers, which subsequently involve the colon. Finally, during what must be considered the experimental phase in the era of evaluation of vagus resection with associated gastroenterostomy, as advocated by Dragstedt et al.⁶ in the treatment of duodenal ulcer, there will be a certain number of cases in which the resection of the vagi will not be permanently effective in altering gastric acidity because of either an inadequate original operation or a possible subsequent regeneration of nerve fibers. Such patients will then present essentially the same anatomic background for fistula formation as those of the earlier period, on whom gastroenterostomy alone was carried out.

ETIOLOGY

Gastrojejunal ulcer is the inevitable precursor of a gastrojejunocolic fistula, but the exact cause of such an ulceration remains as much a matter of debate as the etiology of the duodenal or gastric

*Presented at the annual meeting of the New England Surgical Society, New Haven, Connecticut, October 1, 1948.

From the Surgical Service, Cushing Veterans Administration Hospital and the Massachusetts General Hospital.

Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

[†]Associate in surgery, Harvard Medical School, chief Surgical Service, Cushing Veterans Administration Hospital, associate visiting surgeon, Massachusetts General Hospital.

[‡]Resident in surgery, Cushing Veterans Administration Hospital.

MT AUBURN HOSPITAL

The following public-health lectures will be held at Margaret Jewett Hall, Mt Auburn Hospital, 330 Mt Auburn Street, Cambridge, Massachusetts, on Wednesday evenings at 8 o'clock

- January 19 X-Ray in Modern Medicine Richard Schatzki, M D
 February 2 The Cancer Problem Edward A Cooney, M D
 February 16 The Heart and High Blood Pressure Dudley Merrill, M D
 March 2 Tuberculosis Lowrey F Davenport, M D
 March 16 Surgical Emergencies Stanley J G Nowak, M D

These lectures are open to the public

NATIONAL CONFERENCE ON MEDICAL SERVICE

The National Conference on Medical Service will be held at the Palmer House, Chicago, on February 6. The preliminary program is as follows

- 9 00 a m Registration, Foyer of Red Lacquer Room Fourth Floor Palmer House
 9 30 a m Call to order
 Appointment of Committees
 Address of the President — E F Sladek, M D, Traverse City, Michigan
 9 45 a m Legalized Medical Research
 Medical Problems — Chris J D Zarafonetus, M D, University of Michigan
 Legal Problems — George Wakerlin, M D, University of Illinois
 10 25 a m Title to be announced — James R McVay, M D, Kansas City, Missouri, Chairman, Council on Medical Service, A M A
 10 50 a m Progress of the World Health Organization — Frank Calderone, M D, Director, American Office, World Health Organization
 11 05 a m Progress of the World Medical Association — Creighton Barker, M D, Executive Secretary, Connecticut State Medical Association
 11 20 a m Medical Program of the United Mine Workers of America Welfare and Retirement Fund — Warren F Draper, M D, Executive Medical Director
 11 40 a m Discussion Period
 12 15 p m Subscription Luncheon
 1 00 p m The A M A puts on its Fighting Togs Speaker to be announced
 2 00 p m What's Happening in Washington This Week — James D Boyle, United Public Health League
 2 30 p m Discussion To be opened by Joseph S Lawrence, M D, Director of the Washington Office, A M A
 2 40 p m Panel Discussion on Postgraduate Education of the Doctor —
 (a) Responsibility of Medical Schools in Continued Postgraduate Education of the Doctor — George N Aagaard, Director of Postgraduate Medical Education Program, University of Minnesota
 (b) Function of the State Medical Society in Postgraduate Work — C W Smith, M D, Harrisburg, Pennsylvania
 (c) Survey Findings on Specialization in Colorado — Harold I Goldman, M D, Denver, Colorado
 3 40 p m Discussion Period
 4 00 p m Can Corporations Such as Hospitals Legally Engage in the Practice of Medicine? — Wilbur Bailey, M D, Los Angeles, California
 4 30 p m Report of Committees and Election of Officers
 5 00 p m Adjournment
 (Note All papers will begin exactly as scheduled No speaker will be allowed to speak overtime)
 All physicians are invited

THE AMERICAN CANCER SOCIETY FELLOWSHIPS IN EXFOLIATIVE CYTOLOGY

At the symposium on exfoliative cytologic diagnostic techniques of the American Cancer Society, held in Boston in April, 1948, the opinion was expressed that facilities were urgently needed to train qualified pathologists and clinicians in teaching positions at approved institutions providing residency training in pathology as well as facilities for the training of technicians

At the same time delegates recommended that the American Cancer Society proceed to engage actively the interest and support of institutions and laboratories in setting up such training programs where the best training facilities appeared to be available. Thus inquiries were sent to four teen laboratories over the country and, on the basis of their interest and monies available, grants will be made for fellowship training in ten laboratories to support 23 fellows

The purpose of these fellowships is to provide training in diagnostic techniques in exfoliative cytology for qualified pathologists. It is anticipated that trainees will not assume the role of teachers until sufficient personal experience and competence have been acquired

Fellowships shall be awarded by institutions or laboratories designated by the Society to applicants on the basis of their past training and their intention to teach in their own laboratories diagnostic techniques in exfoliative cytology to interested pathologists, clinicians and technicians

Applicants for fellowships in exfoliative cytology of the American Cancer Society shall be graduates of Class A medical schools of the United States and its territories and of Canada, and be citizens of the United States not over fifty years of age on the next birthday following commencement of fellowship tenure. They shall have completed two years of postgraduate training in pathology and shall conform in other respects to requirements of the institution to which they apply

Each fellowship shall be awarded for a period of four months. Fellowship training shall begin on November 1, 1948, or as soon as possible thereafter. Such fellowships are not subject to renewal

Stipends will be paid in two sums: the first, a grant to the laboratory for tuition, overhead, and other expenses as outlined to the Society; the second, to the trainee partially to cover his board, room and incidentals for the period of training. The latter sum shall amount to \$140 and shall be paid directly to the recipient monthly in advance to avoid payment of income tax for services rendered to the hospital

Individual applicants for fellowships in exfoliative cytology shall apply directly to institutions where fellowships are available. In no instance shall application be made directly to the American Cancer Society

The following fellowships are available

LABORATORY	NUMBER	DIRECTOR
Cornell University Medical College, New York City	6	George N Papanicolaou, M D
Jefferson Hospital, Philadelphia	6	Lewis C Scheffey, M D
University of Oregon Medical School, Portland, Oregon	2	Warren C Hunter, M D
University of California Hospital, San Francisco	2	Herbert F Traut, M D
Michael Reese Hospital, Chicago	2	Otto Saphir, M D
Hartford Hospital, Hartford, Connecticut	2	Ralph E Kendall, M D
New York Post-Graduate Hospital, New York City	1	Locke L Mackenzie, M D
Free Hospital for Women, Brookline, Massachusetts	1	Arthur T Hertig, M D
Mayo Clinic, Rochester, Minnesota	1	John R McDonald, M D

(Notices concluded on page xi)

partial obstruction and dilatation proximal to the fistula

An interesting feature of the lesion is that, as a rule, unless the fistula is very large the folds of jejunal mucosa act as a valve that prevents passage of gastric contents into the colon via the fistula^{3, 24} (Fig 2) but permits the regurgitation of feces and flatus into the jejunum and thence into the stomach. This explains the greater efficacy of barium enemas as compared to barium by mouth for visualizing these fistulas and further suggests why medications are ineffective in combating the diarrhea,

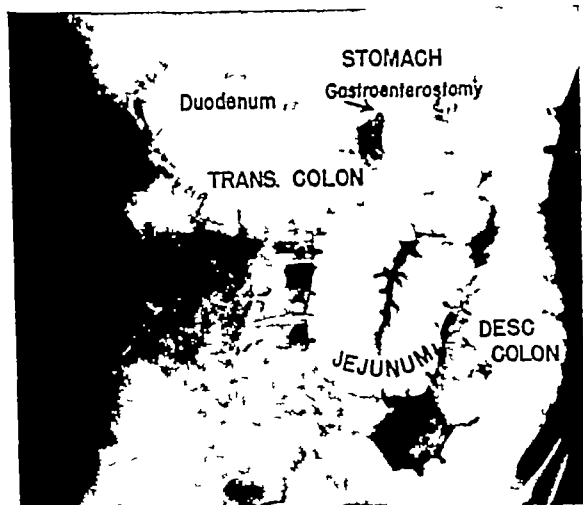


FIGURE 2 Roentgenogram Demonstrating Stomach Filled with Opaque Material after a Barium Enema
No barium passed through the fistula in the reverse direction after gastric studies

whereas a constipating diet is sometimes successful. The mechanism of the diarrhea, with its resulting loss of weight, vitamin deficiency and hypoproteinemia, therefore, is probably irritation of the small intestine by feces and not, as is commonly believed, the direct and rapid passage of gastric contents into the colon.

CLINICAL DATA

All patients were men whose original lesion was a duodenal ulcer. They were first operated on at an average age of thirty-four, approximately five years after their first symptoms, 6 posterior gastroenterostomies, 1 pylorotomy, 1 exclusion operation and 1 Billroth II were the original procedures. An average of nine years supervened before ulcer symptoms recurred, and on the average two years were added before symptoms of a fistula became evident. Even then the symptoms were allowed to persist for approximately a year before operation was carried out, so that these patients, whose ulcer

symptoms usually started in their late twenties, were over forty-five years of age before they were operated on for the fistulas (Table 1).

Weight loss is the most consistent symptom in gastrojejunocolic fistulas (Table 2), being marked and rapid in over 90 per cent of the cases in spite of the fact that anorexia is uncommon. Except in patients with fecal vomiting,²⁴ unimpaired or even increased food intake is the rule.³ Thus, although the appetite in 3 cases was better than usual, and decreased in but 1, 8 patients were strikingly below their normal weight. This weight loss is primarily the result of the watery or semisolid diarrhea found in two thirds of this series, but usually encountered in an even higher proportion.¹⁶ The stools are acid and foul, owing to fatty acids, and, on occasion (as illustrated in 1 of our cases), show recognizable undigested food within an hour of its ingestion. Further manifestations of the diarrhea in two thirds of the cases are weakness, dehydration and emaciation.^{3, 16} Lowered serum protein values in over 80 per cent

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of the cases are reported by Atwater, Butt and Priestly.¹⁶

About half the patients complained of fecal-smelling eructation,^{16, 26} which was a more common finding than foul vomiting, since the passage of gas into the stomach from the colon takes place more readily than intestinal material and does not depend to the same degree on the fluidity of the large-bowel contents.³ Nausea and vomiting were present in 5 cases but both were not always present in the same patient. In the absence of intestinal obstruction, vomitus that is fecal in character is pathognomonic of a gastrocolic fistula.

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ulcer that preceded it. It seems probable that anastomotic ulcers occur when enterostomy or gastric resection fails to control adequately the gastric hyperacidity in a patient with an ulcer diathesis.⁷ The lesions represent the effect in such persons of the unneutralized acid gastric contents on the first part of the small intestine with which they come in contact. Operations for gastric ulcers

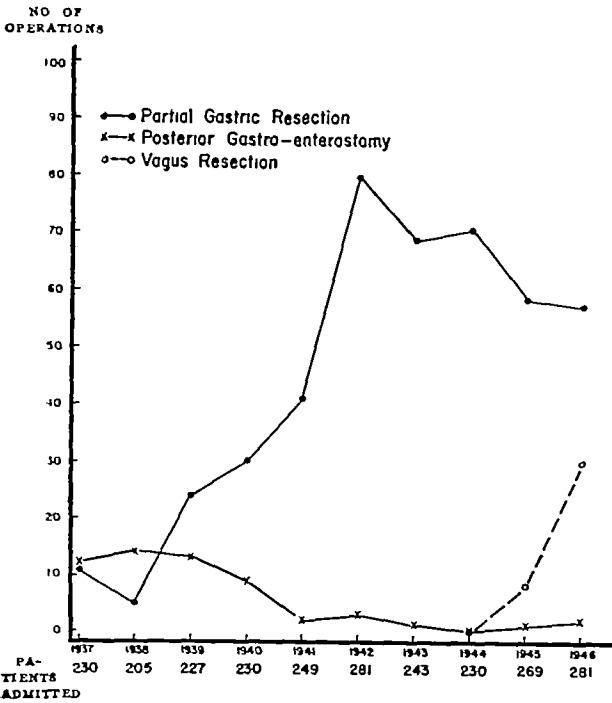


FIGURE 1 Types of Operation for Duodenal Ulcer at the Massachusetts General Hospital, 1937-1946, Showing the Increase in Gastric and Vagus Resections and the Decrease in Gastroenterostomy as the Surgical Treatment of Duodenal Ulcer

A total of twenty-four other types of gastric operations, including plastic procedures and explorations, were done during this period

are seldom attended by this complication, in contradistinction to those for duodenal ulcers.³

The incidence of gastrojejunal ulcers after gastroenterostomy alone varies according to different authors⁸⁻¹⁰ from Verbrugge's⁸ figure of 1.41 per cent to Hurst and Stewart's¹⁰ 51 per cent. Balfour and Down¹¹ report a rate of 3.26 per cent of 500 cases, and Benedict⁵ cites a comparable figure from the Massachusetts General Hospital of 2.9 per cent.

After gastric resection for benign lesions, the incidence of gastrojejunal ulcers is at the lower rate of 0.4 to 10 per cent,¹²⁻¹⁵ and marginal ulcers are essentially never encountered in resections for gastric carcinoma, in which condition hypochlorhydria is the rule. Between 8.7 and 23.8 per cent^{7, 16-22} of all marginal ulcers perforate into the transverse colon, causing gastrojejunocolic fistulas.

The time between the original operation for ulcer and the development of a fistula varies from six

weeks to forty years,^{3, 23} with an average of approximately seven years.^{3, 16, 24} The 9 patients in the present series averaged eleven years (Table 1).

Inasmuch as duodenal ulcers are approximately four times as common in male as in female patients,²⁵ it is not surprising that marginal ulcers, which represent a secondary surgical complication to the condition, are relatively rare in women and that gastrojejunocolic fistulas as a further sequela are almost never encountered.

At the time the diagnosis of gastrojejunocolic fistula was made the average age of our 9 patients was forty-four years, which closely parallels the average reported in larger series of cases,^{3, 26} and the individual variation of thirty-one to fifty-eight years in our cases likewise approaches the span of twenty to seventy-two years found in the literature.^{8, 24}

In the period covered by this paper (1937-1947, inclusive) 5 patients were admitted to the Massachusetts General Hospital in whom gastrocolic fistulas were due to carcinoma, 1 originating in the stomach and the other 4 in the colon. These

TABLE 1 Duration of Symptoms in Relation to Operations

CASE No.	AGE AT ONSET OF FISTULA SYMPTOMS*	SYMPTOM FREE PERIOD FOLLOWING GASTRO-ENTEROSTOMY	PERIOD BETWEEN GASTRO-ENTEROSTOMY AND DEVELOPMENT OF FISTULA	DURATION OF FISTULA SYMPTOMS BEFORE OPERATION
1	37	37	37	4 yr
2	30	None	5	2 yr
3	49	13	15	1 mo
4	49	6	12	1 1/2 yr
5	31	3	6	2 1/2 yr
6	56	6	6	3 mo
7	50	11	11	2 mo
8	39	None	1	3 mo
9	58	30	30	6 mo
	46	9	10	
Average	45	9	11	1 yr 3 1/4 mo

*All patients were men

fistulas as well as those secondary to tuberculosis and other special diseases of the stomach or colon.^{7, 16, 22, 27} are caused by simple direct extension of the pathologic process rather than by any alteration in gastric physiology and are, therefore, not included in the present discussion.

PATHOLOGY

Depending on the site and extent of the anastomotic ulcer, the fistula may be gastrocolic, jejunocolic or gastrojejunocolic. Such fistulas are nearly always single,^{3, 7} although in 1 case there were two, with a jejunal ulcer in addition. The fistulas vary in diameter from a few millimeters to 6 cm.²⁴ and are lined with a smooth mucous membrane, which usually shows no ulceration³ and in which the glands are regularly disposed. The colon is often constricted at the lesion, with resulting

partial obstruction and dilatation proximal to the fistula

An interesting feature of the lesion is that, as a rule, unless the fistula is very large the folds of jejunal mucosa act as a valve that prevents passage of gastric contents into the colon via the fistula^{3 24} (Fig 2) but permits the regurgitation of feces and flatus into the jejunum and thence into the stomach. This explains the greater efficacy of barium enemas as compared to barium by mouth for visualizing these fistulas and further suggests why medications are ineffective in combating the diarrhea,

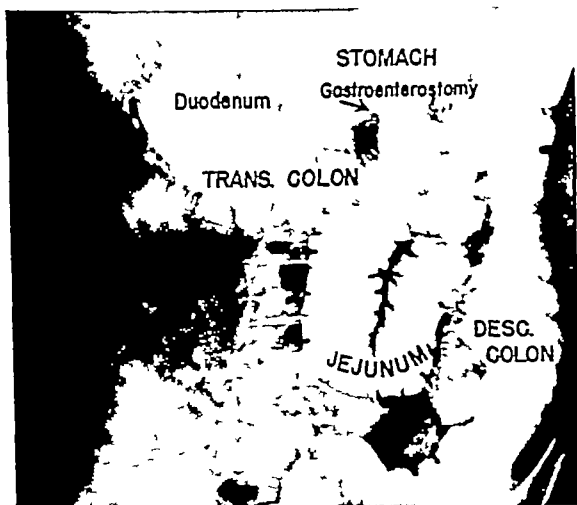


FIGURE 2 Roentgenogram Demonstrating Stomach Filled with Opaque Material after a Barium Enema
No barium passed through the fistula in the reverse direction after gastric studies

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mittently passing into the stomach neutralize the acidity to an unpredictable degree

Abdominal pain is an undependable symptom and is less related to meals, or relief by food and alkali, than the original ulcer discomfort is.¹⁹ Eusterman²⁸ states that in 85 per cent of the cases the pain is referred lower and farther to the left than that typically found with duodenal ulcer. Crampy lower abdominal discomfort accompanies partial large-bowel obstruction or irritation at the site of the lesion, whereas cessation of such pain and the onset of diarrhea suggest relief by the establishment of the fistula. There is little correlation between the location of pain and the finding of tenderness, and, in fact, the physical examination rarely re-

of surgical intervention without which the prognosis in this condition is progressive inanition and an early death from perforation, hemorrhage or intercurrent disease.^{3 8 29 30}

The first objective of treatment is to restore the patient to sufficiently good condition to withstand the formidable operative attack upon the fistula itself. This may be accomplished by medical measures alone if the condition has not persisted so long that emaciation is marked. The importance of intelligent use of blood transfusions, parenteral fluids and chemotherapeutic agents, both as a preliminary and as an adjunct to surgery, cannot be overstressed, and undoubtedly such measures are of prime significance in the marked lowering of the

TABLE 3 Results of Operation *

CASE No	DATE†	ORIGINAL OPERATION	PRELIMINARY OPERATION FOR FISTULA	FISTULA OPERATION FIRST STAGE	FINAL DEFINITIVE OPERATION	OUTCOME
1	1937	Posterior gastroenterostomy	Jejunostomy	—	Gastric resection‡	Relief
2	1938	Posterior gastroenterostomy	—	Excision and restoration	—	Death
3	1938	Exclusion operation	—	—	Gastric resection‡	Relief
4	1939	Bilroth II procedure	Colostomy	—	—	Death
5	1939	Posterior gastroenterostomy	—	Excision and restoration	Gastric resection	Death
6	1940	Posterior gastroenterostomy	Cecostomy	—	—	Death
7	1941	Posterior gastroenterostomy	—	Excision and restoration	Gastric resection	Relief
8	1941	Pylorectomy	—	—	Gastric resection‡	Relief
9	1947	Posterior gastroenterostomy	—	Excision and restoration	Trans thoracic vagotomy	Relief

*A duodenal ulcer was the original lesion in all the cases

†Date of operation for fistula

‡Excision of the fistula was of necessity part of the operation

veals any significant findings except for abdominal scars and evidence of emaciation. Occasionally an inflammatory mass can be felt,^{2 7 26} as in 2 of our cases.

Roentgenologic study of the intestinal tract by barium enema is the most helpful diagnostic procedure. Because of the valve-like action of the jejunal mucosa described above, a barium enema is more likely to demonstrate the fistula than a gastrointestinal series. This fact was emphasized in the report by Gray and Sharpe²⁶ of 49 cases confirmed by operation in which the fistula was revealed in only 13 of the 40 patients who had stomach x-ray films taken, whereas it was shown in all of the 25 studied by barium enema. In the present series, barium enema revealed the lesion in 5 of the 6 cases in which this procedure was carried out, whereas 4 of the 7 gastrointestinal series failed to reveal the fistula.

Enemas to which distinctive coloring matter has been added reveal the condition if the dye can be recovered by gastric lavage, and similar coloring material taken by mouth and found in the stool within a short period is suggestive of the diagnosis.

TREATMENT

There is no satisfactory medical treatment for gastrojejunal fistulas. Few diseases present a greater challenge to the proper timing and selection

mortality rate in recent years. In certain cases, however, the effects of a long period of depletion may be so pronounced that supportive measures alone will be unavailing as adequate preoperative preparation unless the vicious circle of the self-perpetuating diarrhea is interrupted. Pfeiffer³⁰ was the first to emphasize the efficacy of a proximal shunt of the fecal stream to accomplish this end, and his advocacy in 1939 of an ascending colostomy as a preliminary procedure to corrective surgery stands as the most important single contribution to the treatment of gastrojejunal fistulas. With its adoption, the mortality has been reduced from levels as high as 63 per cent³¹ to below 5 per cent,³² and although many other types of side-tracking operations have been advanced by Marshall,¹ Dreosti,¹⁷ Lahey¹⁹ and others, none have proved superior to the originally advocated ascending colostomy in simply achieved effectiveness. Before the period of chemotherapy, peritonitis in these debilitated patients often followed even the simple procedure of colostomy or cecostomy, and 2 of the patients in this series on whom these procedures were carried out died in eight and fourteen days of peritonitis (Table 3).

After the initial treatment by appropriate medical or surgical measures, the problem of interrupting the fistulous tract must be met. This has been accomplished by many surgical procedures, including

simple division and closure of small fistulas, excision of the fistula and gastroenterostomy stoma with substitution of other varying types of gastroenterostomies with and without gastric resection, and *en-bloc* removal of the area of stomach, jejunum and colon involved in the fistulous process with re-establishment of the normal continuity of the intestinal tract. Progress and changes in the field of medicine, including the advent of chemotherapy, have led to certain modifications in the surgery of this condition but have not lessened the technical difficulties invariably presented by an inflammatory mass involving the upper and lower intestinal tract in a region distorted by the adhesions and altered anatomy resulting from the earlier operation.

Of the 7 patients in our series in whom a direct attack was made upon the fistula (1 of whom died of bronchopneumonia four days postoperatively), 4 had a resection of the fistula with restoration of intestinal continuity. In the remaining 3 gastric resection was carried out at the same time the fistula was surgically corrected. Although these patients all survived, there is a very considerable added hazard in this procedure.^{3, 21, 22}

The final phase in the treatment, unless a definitive surgical procedure has already been carried out, lies in dealing surgically with the patient's ulcer tendency, which has so insistently asserted itself by multiple manifestations in the past. With the patient's almost immediate improvement after correction of the fistula, the surgeon is often tempted to postpone further operation indefinitely. Such an attitude shows an understandable but misdirected consideration for the patient, for many reports^{4, 24} bear out the finding that if the intestinal continuity is restored a duodenal ulcer will again develop in from 20²⁴ to 40 per cent¹⁹ of the cases. This proneness to recurrence is well illustrated by the fact that in this series all 3 of the surviving patients in whom the normal anatomy of the intestinal tract was re-established exhibited new duodenal ulcers within three months to a year. All these patients were again operated upon after the recurrence of symptoms, and 1 of them died from peritonitis five days after a gastric exclusion operation.

Selection of a simple gastroenterostomy as the final definitive operation would merely serve to invite a repetition of the unfortunate train of events and would, in addition, show a disregard of the growing tendency to abandon such an operation for the treatment of this condition as pointed out above (Fig 1).

Gastric resection by one of the accepted technics has generally been used as the procedure of choice but is uniquely difficult and hazardous to perform because of adhesions and distortion due to the multiple antecedent operations in these patients. It was to avoid these technical intra-abdominal difficulties that consideration was given to thoracic vagotomy as the definitive operation to

correct the ulcer diathesis in patients without pyloric obstruction.

In the following case this plan of treatment was successfully carried out. So far as we can determine this is the first report of a case in which such an operative policy was adopted, although before the definitive operation cited, the potential role of vagotomy in the treatment of gastrojejunal fistula was also suggested by Barber.³²

CASE REPORT

J C S. (C V A H 1149), a 46-year-old single box maker, was well until the age of 34 years, when he underwent operation for a perforated peptic ulcer. Two years later posterior gastroenterostomy was done. He was then asymptomatic for 9 years, when pain recurred, this time in the left upper quadrant. Nine months later at the age of 46 he developed weakness, faintness and sweating, followed in 1 week by approximately nine bowel movements every night. His

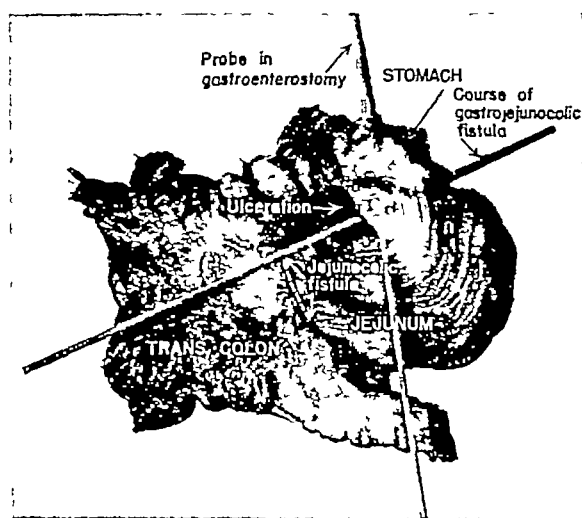


FIGURE 3 Specimen Showing a Fistula 2.5 cm in Diameter Opposite the Gastrojejunal Stoma

The resected portion of stomach is largely obscured by the opened jejunum

nocturnal diarrhea continued for 5 months, during which he lost 20 lb before his first admission to the Cushing Veterans Administration Hospital on December 16, 1946.

Physical examination revealed pallor, moderate emaciation and clubbing of the fingernails. The abdomen was protuberant, and an indefinite upper abdominal mass was palpable. Laboratory examinations were negative, except for a hemoglobin of 12.2 gm, a white-cell count of 14,050 and a total protein of 6.3 gm per 100 cc. Charcoal administered by mouth was passed by rectum in 2 hours and 10 minutes. A barium enema revealed a gastrojejunal fistula (Fig 2), although upper gastrointestinal x-ray studies characteristically failed to reveal the lesion.

Preoperatively, the patient was given 2 gm of sulfathalazine four times a day, and a total of 300,000 units of penicillin intramuscularly. The posterior gastroenterostomy and fistula were excised *en masse* (Fig 3), including a segment of the greater curvature of the stomach. The stomach was closed, and the continuity of the jejunum and of the colon was re-established by means of end-to-end anastomoses. The gastrojejunal fistula was 2.5 cm in diameter and opposite the gastrojejunal stoma, which was of similar size.

The postoperative course was uneventful. X-ray examination of the upper gastrointestinal tract 1 month after a leave from the hospital showed no evidence of ulcer. The fasting

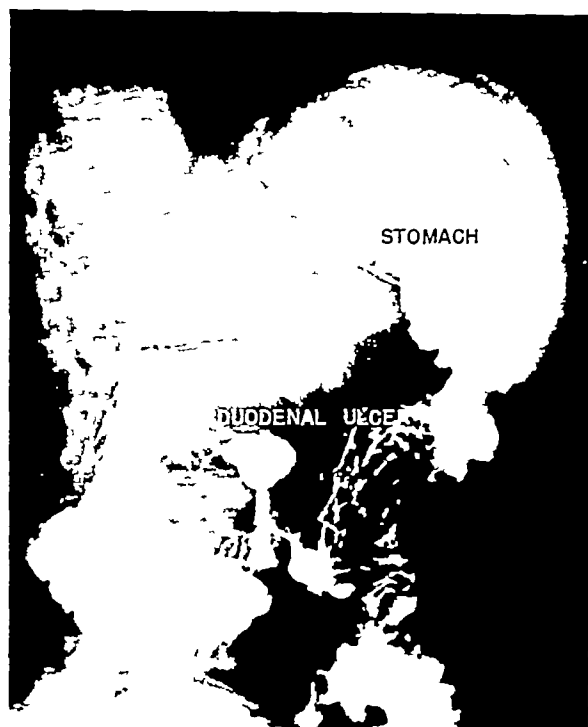


FIGURE 4 Duodenal Ulcer Developing Three Months after Restoration of Intestinal Continuity Following Excision of a Gastrojejunal Colic Fistula

gastric content contained no free hydrochloric acid and 10° of total acidity. He was discharged and readmitted 1 month later because of a 2-week history of right-upper-quadrant

showed an ulcer crater, 1 by 2 cm, in the duodenal cap (Fig 4). A transthoracic vagus resection was done.

On the 18th postoperative day the patient had hematemesis, followed by melena. He continued to bleed for 5 days, during which he received 5½ pints of blood. Two months later there was no x-ray evidence of ulcer, and the insulin test (Fig 5) was consistent with complete vagus resection. One and a half years after the excision of the fistula and one year after the vagus resection he was asymptomatic and had well healed abdominal and thoracic scars. No free acid was secreted after insulin hypoglycemia. X-ray examination revealed no evidence of ulcer. The patient had gained back his 20 pounds in weight.

DISCUSSION

The case reported above re-emphasizes a number of fundamental considerations and introduces certain factors for further speculation. In the first place, the initial satisfactory response following extirpation of the fistula without a preliminary colostomy bears out the fact that, if the patient's condition is satisfactory, a first-stage operation with its inevitable soiling of the abdominal wall and need of eventual closure may be unnecessary. In case of doubt, however, such a procedure should be performed, but even this may be unavailing in avoiding a fatal outcome, as illustrated by Cases 4 and 6 in our series, if the patient's general condition is below a critical level.

A second fact illustrated by the case cited is that, if intestinal continuity is restored, the patient may develop an ulcer even though his progress is being followed by frequent visits, and thus he may be a less favorable candidate for a definitive surgical procedure than he would have been had such a final step been taken before discharge from the hospital.

Another interesting fact is the massive intestinal hemorrhage, presumably from the reactivated duodenal lesion that occurred eighteen days after vagotomy. After such an interval, it would be expected that, if the operation had been effective, healing of the ulcer would have progressed to a stage at which bleeding could not well have occurred. There can be little doubt from the findings of the insulin test, as well as the fact that both vagi were resected from 8 cm above the diaphragm to below the point at which they arborize, that the procedure had interrupted all impulses that might have reached the stomach over these nerves.

The possibility of performing vagotomy by the subdiaphragmatic route at the time the fistula is excised is naturally one that must be considered. The fact that it spares the patient further surgical treatment is an obvious advantage but one that seems to be more than outweighed by the possible contamination of the vulnerable subdiaphragmatic area by the potential soiling attendant on carrying out the anastomosis of the transverse colon. It is important to remember that with excision of the fistula and restoration of the intestinal tract there is bound to be a brief respite from ulcer symptoms during which the patient's general condition can

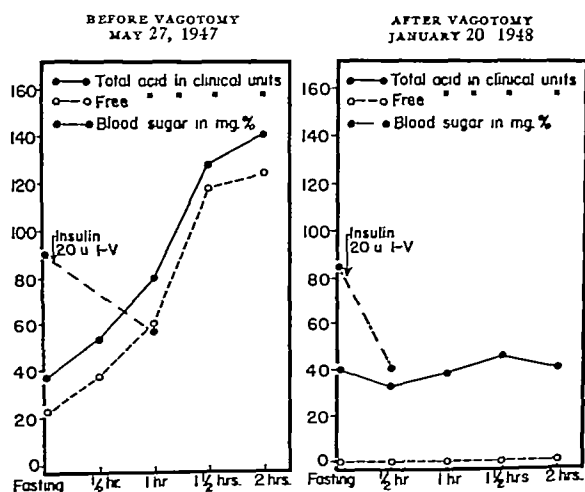


FIGURE 5 Insulin Tests before and after Vagotomy, Showing the Absence of Increased Acidity that Followed Insulin Hypoglycemia as an Indication of the Effectiveness of Vagus Resection

pain. He now had tenderness over the right upper quadrant and the fasting gastric content contained 51° of free hydrochloric acid and a total acidity of 75°. X-ray examination

still further improve before he is again subjected to the added risk of a definitive surgical operation. Furthermore, there are apt to be technical difficulties in satisfactorily exposing the esophageal hiatus by the subdiaphragmatic route because of adhesions from the previous operation and existing inflammatory reaction. These difficulties are obviated by a transthoracic approach to the final operation, and in such cases vagotomy can probably be carried out most effectively by such a route.³⁵

SUMMARY AND CONCLUSIONS

The findings in 9 cases of gastrojejunocolic fistula are presented, and the literature on the subject is reviewed.

The symptomatology is usually attributable to the secondary effects of diarrhea induced by the reflux of irritating large-bowel contents into the upper jejunum and stomach. Passage of gastric material into the colon through the fistula in the reverse direction is delayed, as a rule, by a valve-like action of the jejunal mucosa.

The treatment of gastrojejunocolic fistulas is surgical and consists of removing the fistula, restoring bowel continuity and correcting the ulcer diathesis.

Preparation of the patient for excision of the fistula should include the institution of an ascending colostomy as recommended by Pfeiffer as a preliminary procedure in all patients whose general condition is unsatisfactory.

The tendency in these patients to reactivate an ulcer after an excision of the fistula and restoration of intestinal continuity is so strong that unless corrective surgical measures have been carried out at the earlier operation they should be adopted before the patient is finally discharged from the hospital.

A case is cited for the first time in which, after excision of the fistula, transthoracic vagotomy was used as the definitive treatment of the ulcer diathesis. This patient was asymptomatic a year after the vagus resection.

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The postoperative course was uneventful. X-ray examination of the upper gastrointestinal tract 1 month after a leave from the hospital showed no evidence of ulcer. The fasting

showed an ulcer crater, 1 by 2 cm, in the duodenal cap (Fig 4). A transthoracic vagus resection was done.

On the 18th postoperative day the patient had hematemesis, followed by melena. He continued to bleed for 5 days, during which he received $5\frac{1}{2}$ pints of blood. Two months later there was no x-ray evidence of ulcer, and the insulin test (Fig 5) was consistent with complete vagus resection. One and a half years after the excision of the fistula and one year after the vagus resection he was asymptomatic and had well healed abdominal and thoracic scars. No free acid was secreted after insulin hypoglycemia. X-ray examination revealed no evidence of ulcer. The patient had gained back his 20 pounds in weight.

DISCUSSION

The case reported above re-emphasizes a number of fundamental considerations and introduces certain factors for further speculation. In the first place, the initial satisfactory response following extirpation of the fistula without a preliminary colostomy bears out the fact that, if the patient's condition is satisfactory, a first-stage operation with its inevitable soiling of the abdominal wall and need of eventual closure may be unnecessary. In case of doubt, however, such a procedure should be performed, but even this may be unavailing in avoiding a fatal outcome, as illustrated by Cases 4 and 6 in our series, if the patient's general condition is below a critical level.

A second fact illustrated by the case cited is that, if intestinal continuity is restored, the patient may develop an ulcer even though his progress is being followed by frequent visits, and thus he may be a less favorable candidate for a definitive surgical procedure than he would have been had such a final step been taken before discharge from the hospital.

Another interesting fact is the massive intestinal hemorrhage, presumably from the reactivated duodenal lesion that occurred eighteen days after vagotomy. After such an interval, it would be expected that, if the operation had been effective, healing of the ulcer would have progressed to a stage at which bleeding could not well have occurred. There can be little doubt from the findings of the insulin test, as well as the fact that both vagi were resected from 8 cm above the diaphragm to below the point at which they arborize, that the procedure had interrupted all impulses that might have reached the stomach over these nerves.

The possibility of performing vagotomy by the subdiaphragmatic route at the time the fistula is excised is naturally one that must be considered. The fact that it spares the patient further surgical treatment is an obvious advantage but one that seems to be more than outweighed by the possible contamination of the vulnerable subdiaphragmatic area by the potential soiling attendant on carrying out the anastomosis of the transverse colon. It is important to remember that with excision of the fistula and restoration of the intestinal tract there is bound to be a brief respite from ulcer symptoms during which the patient's general condition can

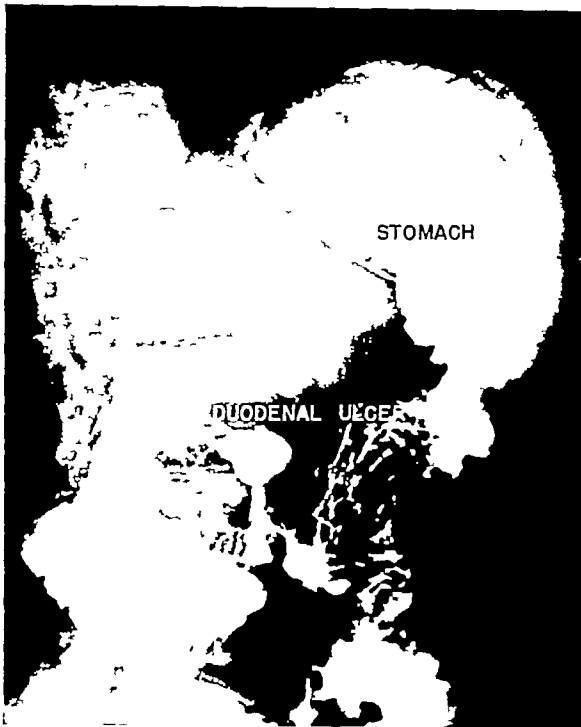


FIGURE 4 Duodenal Ulcer Developing Three Months after Restoration of Intestinal Continuity Following Excision of a Gastrojejunocolic Fistula

gastric content contained no free hydrochloric acid and 10° of total acidity. He was discharged and readmitted 1 month later because of a 2-week history of right-upper-quadrant

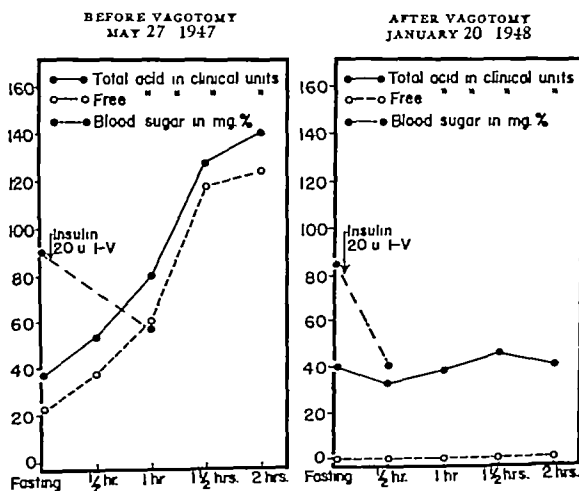


FIGURE 5 Insulin Tests before and after Vagotomy, Showing the Absence of Increased Acidity that Followed Insulin Hypoglycemia as an Indication of the Effectiveness of Vagus Resection

pain. He now had tenderness over the right upper quadrant and the fasting gastric content contained 51° of free hydrochloric acid and a total acidity of 75°. X-ray examination

exacerbation, and the cephalin-cholesterol flocculation was +++

CASE 2 M G, a 20-year-old student nurse, was admitted to the hospital on November 24, 1947, complaining of vague abdominal distress consisting of "fullness" and aching in the upper abdomen associated with frequent eructation of 6 days' duration. This was followed by nausea without vomiting and anorexia so that she had eaten little or nothing for 24 to 36 hours prior to admission; moreover, the mere sight of food nauseated her. On each of three successive days, prior to admission, she had noticed "light, almost clay-colored stools" — no change in the color of the urine had been noted. In addition to these findings she had been listless and depressed.

There was no history of plasma or blood infusion or inoculations within 6 months or exposure to chemicals. She was,

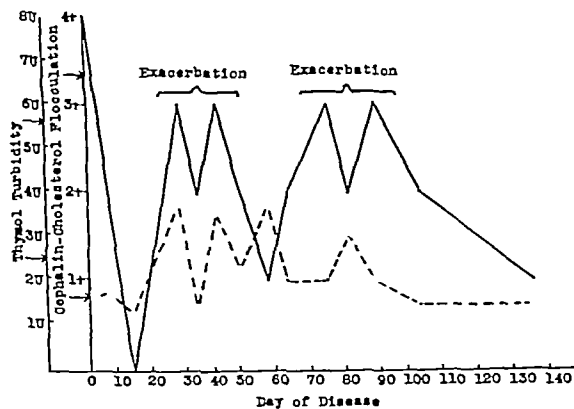


FIGURE 2 Relation of Liver Function to Clinical Course in Case 2

however, quartered in the same building as the patient in Case 1.

The family and past histories and a system review were all noncontributory to the present illness.

Physical examination revealed a well developed, well nourished patient, who was not acutely ill. Examination showed normal findings except for tenderness without spasm in the right upper quadrant. The liver and spleen were not palpable, but there was tenderness to jarring over the right lower thoracic cage.

The temperature was 99°F, the pulse 80, and the blood pressure 110/80.

On November 24 the white-cell count was 7500, with 32 per cent neutrophils and 64 per cent lymphocytes. The erythrocyte sedimentation rate was 21 mm per hour. The urine was negative for bile, and urobilinogen was present in a dilution of 1:8. The icteric index was 11 units. The prothrombin time was 78 per cent of normal. The cephalin-cholesterol flocculation was +++++, and the thymol turbidity was 16 units. The heterophil-antibody agglutination was negative, as were a gall-bladder and a gastrointestinal series. Subsequent liver-function tests are recorded in Figure 2.

The treatment was the same as that in Case 1.

Within a few days of admission the right-upper-quadrant distress became more marked and more sharply localized, and at the same time the patient complained of aching in the left upper quadrant. Examination revealed a palpable, tender spleen. There was a 6-lb weight loss in 2 weeks. On December 8 she felt much better — that is, the right-upper-quadrant tenderness had markedly diminished, and the spleen was no longer palpable. From this time on gradual improvement was noted, and she was discharged on December 20 to the care of her parents, who had been instructed regarding convalescence.

The patient was readmitted 8 days after discharge, complaining of recurrence of fatigue, anorexia, nausea without vomiting and distress in both upper quadrants.

Physical examination was essentially the same as on the previous admission, showing tenderness without spasm to palpation in both upper quadrants associated with tenderness to jarring over the right lower and left lower thoracic cage. The temperature was 99.4°F.

The only significant laboratory findings were a cephalin-cholesterol flocculation of +++ and a thymol turbidity test of 3.7 units on the day of discharge, on the day of readmission these values were, respectively, ++ and 1.3 units. Subsequent liver-function tests are recorded in Figure 2. Cerebrospinal-fluid examination, which was done for reasons explained below, showed a protein of 45 mg per 100 cc. but no cells.

The treatment was the same as that on the previous admission.

There were three well defined exacerbations, manifested by nausea, anorexia, general malaise, headache and increased distress in the upper quadrants, with increased tenderness to palpation. The spleen was occasionally palpable, but the liver was not felt. The exacerbations were rather accurately reflected by the liver-function tests.

On January 17, 1948, because of persistent headache, a lumbar puncture was done to rule out a complicating encephalitis and the findings were as listed above. On January 25 the patient began to feel better as manifested by amelioration of symptoms and abdominal tenderness. She was discharged but has been followed as an outpatient, and her course has been one of slow gradual improvement. She was back on duty 4½ months after the onset of illness.

CASE 3 N S, a 21-year-old student nurse, was admitted to the hospital on November 17, 1947, complaining of nausea and lack of appetite of 5 days' duration. She had not been well for 2 or 3 months before admission because of fatigue and weakness, but repeated examinations at sick call had been negative. Four or five days prior to admission, however, a

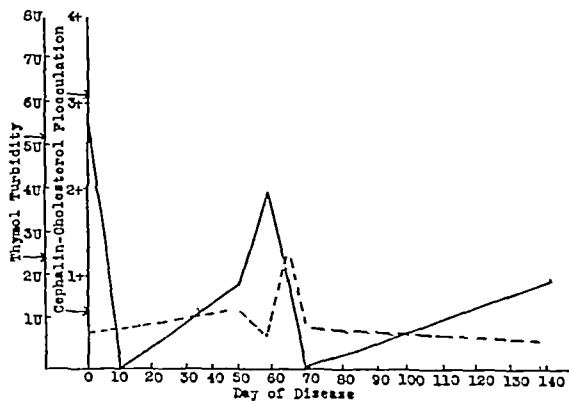


FIGURE 3 Relation of Liver Function to Clinical Course in Case 3

decided change had occurred in the form of intense nausea without vomiting, general malaise, anorexia with an aversion to food and marked fatigue.

There was no history of plasma or blood infusion, inoculations or exposure to chemicals within the last 6 months. The patient, being a student nurse, was quartered in the same building as the patients in Cases 1 and 2.

The family and past histories and a system review were noncontributory to the present illness.

Physical examination revealed a well developed, well nourished patient, who was not acutely ill but appeared rather listless. Complete examination disclosed normal findings except for tenderness to palpation in a sharply localized area in the right upper quadrant. There was no associated muscle spasm, but there was tenderness to jarring over the right lower thoracic cage. The liver and spleen were not palpable, and there was no lymphadenopathy.

The temperature was 99.2°F, the pulse 80, and the blood pressure 110/72.

HEPATITIS WITHOUT JAUNDICE AND WITHOUT HEPATOMEGLY

T. J. DOMENICI, M.D.*

MALDEN, MASSACHUSETTS

FOUR cases of hepatitis without jaundice and without hepatomegaly constitute the material of this report. Hepatitis without jaundice has been variously described as a "mild disease"¹ and "mild non-icteric form of hepatitis,"² running a course of six to eight weeks. A review of the literature reveals that an enlarged and tender liver is an essential finding in virus hepatitis and in the hepatitis seen in infectious mononucleosis. The cases presented below were severe illnesses running a four to six months' course. The liver was not enlarged, but instead a sharply circumscribed area of localized tenderness in the right upper quadrant was elicited in all cases. The protracted course, marked by exacerbations and remissions, was associated with marked psychologic turmoil. Whether this fact was an integral part of the disease or a consequence of chronic illness remains open to question. At any rate, irrespective of source, the management of this aspect of the illness proved to be most difficult and is worthy of emphasis.

CASE REPORTS

CASE 1 D. G., a 20-year-old student nurse, was first admitted to the hospital on November 10, 1947, complaining of aching pain in the right upper abdomen, nausea at sight of food, loss of appetite and vomiting of 4 days' duration. She

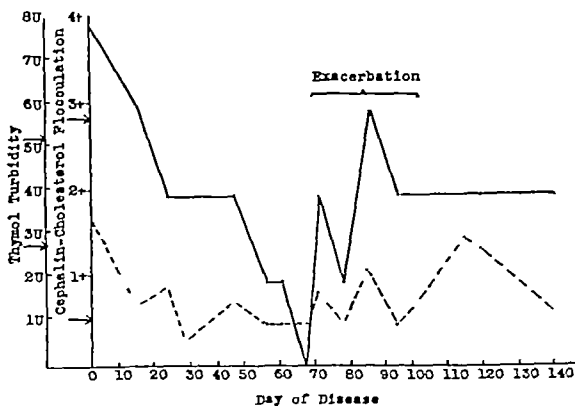


FIGURE 1 Relation of Liver Function to Clinical Course in Case 1

was seen, as an outpatient, at the onset of illness, on the Surgical Service and after twenty-four hours it was decided that surgical treatment was not indicated. The white-cell count at that time was 13,400, with 82 per cent neutrophils.

The patient had not received plasma, blood or inoculations within the 6 months prior to admission. There was no known exposure to chemicals or to patients with virus hepatitis.

*Resident in medicine, Malden Hospital.

The family and past histories and a system review were all noncontributory to the present illness.

Physical examination revealed a well developed, well nourished patient who was not acutely ill. Complete examination revealed normal findings except for a sharply circumscribed area of localized tenderness without spasm in the right upper quadrant just lateral to the midline. This was associated with tenderness to jarring over the right lower thoracic cage. The liver and spleen were not palpable, and there was no lymphadenopathy.

The temperature was 99°F, the pulse 80, and the blood pressure 126/84.

On November 11 the white-cell count was 8000, with 38 per cent neutrophils and 40 per cent lymphocytes. The erythrocyte sedimentation rate was 14 mm per hour. The urine was negative for bile, and urobilinogen was present in a dilution of 1:16 (normal 1:8). The icteric index was 5 units, the prothrombin time was 68 per cent of normal. The initial cephalin-cholesterol flocculation was +++, and the thymol turbidity was 3.5 units (normal 2 units).³ The prothrombin time, after 1 week, was 82 per cent of normal and remained above this value for the duration of the hospital stay. Urinary urobilinogen varied from 1:4 to 1:16, and the white-cell count from 6000 to 8000, with 35-40 per cent lymphocytes. The heterophil-antibody agglutination and gall-bladder and gastrointestinal series were negative. Erythrocyte sedimentation remained within normal limits. Repeat cephalin-cholesterol flocculation and the thymol turbidity tests during both periods of hospitalization are shown in Figure 1.

Glucose (5 per cent) in physiologic saline solution and protein hydrolysate were given intravenously in the first 60 to 72 hours because of almost complete anorexia and vomiting. Subsequent treatment consisted of absolute bed rest, a diet consisting of 250 gm of carbohydrate, 100 gm of protein and 80 gm of fat, multi-vitamins, components of the vitamin B complex and vitamin K in therapeutic doses daily and supplementary high-protein drinks. At first methionine and choline (1 gm each, three times daily) were given, but they were discontinued within 3 to 4 weeks, partly because of inability to disguise the amino acid in a palatable drink.

The appetite remained poor, and there was a 15-lb weight loss in 1 month. The clinical course was characterized by exacerbations manifested by anorexia, nausea, general malaise and increased tenderness in the right upper quadrant. In some instances this was reflected by a rise in the cephalin-cholesterol flocculation and thymol turbidity tests. After 6 weeks it seemed that the patient had reached a *status quo* and she was discharged on December 24 to the care of her family, who had received careful and detailed instructions regarding convalescence.

The patient was readmitted on December 30 complaining of severe anorexia, continuing weight loss, overwhelming and seemingly progressive fatigue and varying right-upper quadrant distress.

Physical examination revealed evidence of further weight loss to 110 lb, and the positive findings consisted of tenderness to palpation in the right upper quadrant in exactly the same area described in the previous physical examination. This was again associated with tenderness to jarring over the right lower thoracic cage.

The cephalin-cholesterol flocculation was ++, though the thymol turbidity was within normal range, being 1.3 units. There were no other significant findings.

The therapeutic measures employed were essentially the same as those for the previous hospitalization.

The patient was again discharged on February 19, 1948, when it seemed that she had started to improve—that is, her appetite was better, the right-upper-quadrant tenderness was minimal, and there had been a slow weight gain of 2 lb. Approximately 7 to 10 days after discharge she suffered another exacerbation. She returned for a trial on duty on April 23, approximately 5½ months after the onset of the illness. However, after 1 month on duty, she suffered another

early symptom and may be severe enough to result in significant weight loss. Appetite and weight loss are only painstakingly regained. The long, rather than short, course makes subsequent chronic liver disease, as mentioned by Chaikin and Chlenoff,⁷ an eminent possibility.

The long course of the illness was attended by marked psychologic disturbance, which, to say the least, complicates the management and treatment. The constant urging and prodding to "eat more" soon engenders in the patient an antagonism for food manifested by a mildly belligerent insistence that "I'm eating as much as I can." The weight lost was only slowly regained, if at all. With prolonged bed rest time soon weighs heavy, particularly in young vigorous adults. Attempts to counteract this by means of occupational therapy were, on the whole, only partially successful.

The cephalin-cholesterol flocculation as mentioned by others⁸⁻¹¹ proved to be a sensitive and reliable test and seemed to bear a relation to the clinical course. The thymol turbidity did not reach the high values reported elsewhere but did show a delayed rise occurring after clinical manifestations of activity.¹²⁻¹⁴

The negative heterophil-antibody agglutination, the absence of lymphadenopathy and the absence of the "atypical" lymphocyte of infectious mononucleosis seem to rule out that disease. The negative history regarding plasma or blood infusions and inoculations, for six months prior to onset of illness, eliminates homologous serum jaundice as a possibility.

SUMMARY

Four cases of hepatitis without jaundice and without hepatomegaly are presented. The finding

of a sharply circumscribed area of localized tenderness in the right upper quadrant was elicited in all cases and appeared to be as significant as a palpable liver.

The course of the disease was long and severe and resulted in the appearance of functional factors that proved difficult to manage.

The cephalin-cholesterol flocculation seemed to be the most sensitive and reliable index of both the liver function and the clinical course.

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On November 18 the white-cell count was 5400, with 59 per cent neutrophils and 31 per cent lymphocytes. The sedimentation rate was 17 mm per hour. The icteric index was 6 units. The prothrombin time was 67 per cent of normal. The urine was negative for bile, and urobilinogen was present in a dilution of 1:8. The cephalin-cholesterol flocculation was +++, and the thymol turbidity was 0.8 units. Repeat performances of these tests at regular intervals yielded normal values, and subsequent liver-function tests are recorded in Figure 3.

Except for minor variations, therapy was the same as that described for Cases 1 and 2.

This patient's illness was a comparatively mild one, though for the first 10 days, anorexia and right-upper-quadrant distress were quite marked. The discomfort gradually subsided, however, and the appetite returned slowly after a minimal loss of weight. The patient was discharged to her home for further convalescence.

She was readmitted 3 weeks after discharge, with a history of a bout of diarrhea beginning 2 days after discharge and consisting of 4 or 5 loose, nonbloody stools daily, without cramps, that lasted for 5 days. Subsequently, she became anorexic, and right-upper-quadrant distress returned.

Physical examination was negative except for a temperature of 99.2°F, and minimal tenderness to palpation in the right upper quadrant.

Laboratory findings of significance were a cephalin-cholesterol flocculation of +, a thymol turbidity of 1.4 units and a prothrombin time 66 per cent of normal. Gall-bladder and gastrointestinal series were negative. Heterophil-antibody agglutination was also negative. The prothrombin time after 10 days of vitamin K therapy was 88 per cent of normal.

The same treatment as on the previous admission was given.

Again, this patient's illness was comparatively mild, though prolonged. Her appetite gradually returned, and right-upper-quadrant tenderness remained minimal. From then on improvement was gradual and without exacerbations. She was discharged on January 27, and she returned to duty 4 months after the onset of the illness.

CASE 4 R. K., a 29-year-old graduate nurse, was admitted to the hospital on November 26, 1947, complaining of loss of appetite, nausea, general malaise and lassitude of 3 days' duration. This patient was charge nurse on the pediatric

ized area of tenderness in the right upper quadrant associated with tenderness to jarring over the right lower thoracic cage. The liver and spleen were not palpable, and there was no lymphadenopathy.

The temperature was 99.6°F, the pulse 74, and the blood pressure 100/60.

On November 26 the white-cell count was 6500, with 63 per cent neutrophils and 32 per cent lymphocytes. The sedimentation rate was 21 mm per hour. The icteric index was 5 units, the prothrombin time was 80 per cent of normal. The urine was negative for bile, and urobilinogen was present in a dilution of 1:4 to 1:8. Cephalin-cholesterol flocculation was +++, and the thymol turbidity was 2.1 units. Periodic performance of the above tests were all normal, and subsequent liver-function tests are recorded in Figure 4.

The treatment was the same as that for the 3 previous cases.

Clinically, there was marked anorexia, nausea, right-upper-quadrant tenderness and a 12-lb weight loss in 2 weeks. After approximately 3 weeks the patient began to improve—that is, the appetite returned, right-upper-quadrant tenderness diminished, and there was a slow gain in weight. She was discharged to her home on December 24. Blood taken on the day of discharge, however, revealed a +++ cephalin-cholesterol flocculation and 2.6-unit thymol turbidity. She was followed at home, and for the first 6 weeks there she did not fare well: the appetite was poor, nausea recurred, tenderness in the right upper quadrant returned and her weight dropped to 90 lb (the weight at the onset of the illness having been 100 lb). Within a week there was decided improvement, which has been progressive except for one minor setback. She has not, however, regained her lost weight and at present she weighs 92 lb. At this writing, 3 months after the onset of the illness, she is not yet ready to work.

EPIDEMIOLOGY

It is perhaps fair to assume that Case 1 was the source of infection for the remaining 3. The source of infection for the first case, however, was not known. The history, as elicited, rules out plasma or blood infusions, chemicals and inoculations. All 4 patients lived in the same building, and the fact that only 3, out of about 50 persons, succumbed to exposure to the first case is perhaps best explained according to Newman⁴—that is, the liver is phasic in activity, and hence susceptibility to infection is variable, thus the phase of susceptibility at time of exposure determines whether or not a person will succumb to infection.

DISCUSSION

The presence of an enlarged liver is mentioned in all articles on hepatitis without jaundice.^{1,2,5,6} As mentioned above the liver was not palpable in this group of cases. There was, however, in each case a sharply localized area of tenderness in the right upper quadrant toward the midline, and this was associated with tenderness to jarring over the right lower thoracic cage. This finding, in my experience, was as significant as an enlarged liver and served as a reliable index to the clinical state.

The clinical course is marked by exacerbations and remissions characterized by varying degrees of anorexia, fluctuating intensity of right-upper-quadrant tenderness and varying degrees of generalized malaise. Some exacerbations are accompanied by a rise in temperature. Anorexia is a constant and

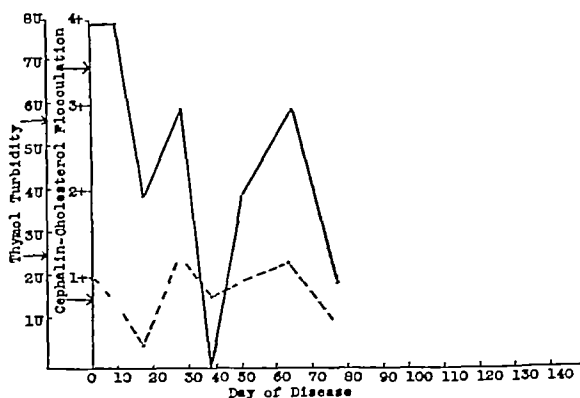


FIGURE 4 Relation of Liver Function to Clinical Course in Case 4

floor where 2 of the other 3 patients had worked, and she had been active in the care of these patients.

There was no history of plasma or blood infusion, inoculations or exposure to chemicals within the last 6 months.

The family and past histories and a system review were noncontributory to the present illness.

Physical examination revealed a well developed, well nourished woman who was not acutely ill. Complete examination disclosed normal findings except for a definite, sharply local-

was dazed but not made unconscious. Later, he had some fever and vomited. He was fairly well until twenty-four hours later, when he became first drowsy and then unconscious, with paralysis of the right arm, leg and face. The right pupil was larger than the left, but reacted to light, there was incontinence of urine and feces, and pressure on a contusion behind the left ear caused crying. Nine hours later he was partially conscious and was regaining the use of the paralyzed muscles, so that operation was delayed. Six days after the accident he was completely well, except for a complicating sore throat, which was considered to be a coincidence. The third report, also by Walton,² concerned a three-and-a-half-year-old girl who was thrown to the floor from a small swing and struck her head. She was dazed, and later vomited. On the following day she had paralysis of the left arm, and exploration of the head was advised. Overcrowding of the hospital caused a delay of twelve hours, by which time she seemed much better and was beginning to use the left hand, so that no operation was done. Her convalescence was rapid, and she made a quick and complete recovery, being entirely well when seen two years later. Walton regards these patients as having had subarachnoid serous exudation and says

That a more or less diffuse oedema, whether involving the subarachnoid cavity or the brain itself, or both, and whether accompanied or not by marked laceration, may play a part in prolonging the general symptoms of concussion, seems a not improbable supposition, it is not, however, of this class of cases that I would speak at length, but rather of those cases in which a local paralysis of more or less temporary nature accompanies such general symptoms, the pathology being here, I apprehend, a local accumulation of fluid under the arachnoid resulting from rapid exudation at the point of most marked bruising, whether the result of direct violence or of contrecoup. For the unilateral paralysis there seems absolutely no plausible explanation, except the pressure of the fluid, and the relief of paralysis was apparently due to relief of this pressure. This lesson is to be particularly borne in mind in the case of children and young adults, and perhaps in alcoholic patients. In elderly patients the same set of symptoms points more decidedly toward hemorrhage.

Cushing³ discusses the physiologic effects of acute compression and states

We must continually bear in mind the difference between a local and a general increase in tension. Inasmuch as the pressure effects of a local process are greater in its immediate neighborhood than at a distance, and inasmuch also as there is considerable pressure discontinuity between the three intracranial compartments, owing to the fairly rigid partitions formed by the falx and tentorium cerebelli, a local pressure, let us say over one hemisphere, may exceed the local arterial pressure and lead to a local anemia sufficient to throw the adjoining parts of the brain out of function without seriously affecting the other hemisphere or the subtentorial structures, of which the medulla is of prime importance.

And in considering extradural and subdural hemorrhage, he says "Confusion may arise in certain cases, owing to the fact that acute, traumatic cerebral edema may closely simulate the general pressure phenomena which accompany actual extravasations of blood."⁴

Current authorities on head injuries recognize the existence of states imitating extradural bleeding, but do not lay great stress upon them. Munro^{5, 6} remarks

In children, hemiplegia and convulsions commonly occur in uncomplicated cerebral oedema. There appears to be a type of malignant and sometimes strictly localized oedema of the brain that will present expansive characteristics. I have usually seen it develop as a postoperative complication.

Rowbotham⁷ believes that interval hemiplegias may be caused by edema, among other conditions. Brock⁸ writes "For rare instances of so-called malignant edema which develop rapidly and do not respond to ordinary methods of dehydration and repeated lumbar puncture, exploratory trephine will have to be resorted to, to rule out meningeal hemorrhage." Gross and Ehrlich⁹ deny the existence of a process such as that assumed above and say

Focal edema of the brain with the development of localizing signs and symptoms which simulate a middle meningeal hemorrhage, has been postulated by numerous observers. This has been used to justify exploration when middle meningeal hemorrhage has been sought and not found, and yet recovery has ensued. It is possible that an extradural clot may be confined over the occipital or occipito-parietal area, more rarely its situation may be far anterior. The improvement following negative exploration can probably be attributed to the decompressive effects concomitant with opening of the dura mater. This serves to prevent fatal cerebral compression. With the tiding over of the critical period, life is sustained, and as the epidural clot slowly reabsorbs, recovery takes place.

At the Rhode Island Hospital, during the past five years, we have treated a total of 8 patients on whom we made the diagnosis of acute focal edema of the brain. The ages varied from ten months to eleven years, we have seen no clear-cut case in an adult. In the same period we have had over 500 children with head injuries, so that the incidence in our experience is low, being well under 2 per cent. Seven of these children were boys. In most cases the child fell and struck his head on the floor or the ground. Linear fracture of the vault, without depression, was present in 3 cases, in 1 of which there was an additional fracture of the maxilla. There was initial unconsciousness in 3 patients. The interval between the injury and the onset of focal signs varied from fifteen minutes to six hours. The focal signs included one-sided reflex changes indicating cortical involvement, Jacksonian convulsive movements and in 1 patient a combination of Jacksonian and generalized convulsions, and one-sided paralyses of varying degrees. Traumatic shock was present in only 2 patients.

It is our practice not to do a lumbar puncture in the presence of shock or when acute extradural or subdural bleeding is suspected, for fear of lessening intracranial pressure and thus increasing bleeding, for these reasons, the cerebrospinal-fluid findings during the active phase of this condition are not available. Punctures done during

ACUTE FOCAL EDEMA OF THE BRAIN IN CHILDREN WITH HEAD INJURIES*

WILFRED PICKLES, M D †

PROVIDENCE, RHODE ISLAND

ON MARCH 18, 1943, the very active two-and-a-half-year-old son of a surgical colleague fell from his high chair with such force that his head bounced on the floor. He seemed dazed for a moment or two but had no definite period of unconsciousness. He cried loudly for a few minutes, as one might expect, but soon seemed to forget all about the fall and was apparently as well as ever. He ate his supper with a good appetite, and was put to bed. Two hours later he began to vomit, he was very pale and his skin was moist and cold, and he was very drowsy, with occasional convulsive twitchings of the right arm and leg. His mother, who is a nurse, believed that he had a severe head injury, so he was taken at once to the hospital. On arrival he was found to be in shock, with poor peripheral circulation and a low temperature, he was semicomatose and had greatly depressed reflexes and motor power of the right arm and leg, and he was admitted with the diagnosis of extradural hemorrhage as a dangerously ill patient. Treatment for traumatic shock was started, and preparations for a cranial exploration were got under way. At about the time when these were completed his condition began to improve, the signs of shock lessened, the semi-coma lightened, the reflexes on the right side became more active, and he moved his arm and leg with more power. In four hours he was so much better that it was evident that exploration would not be needed, and by the next morning, some sixteen hours after the injury, he was fully conscious and happy, with no evident neurologic abnormality. X-ray films of the skull showed no fracture. About a week later a mild bronchopneumonia, which responded well to treatment with sulfadiazine, developed. Recovery was otherwise without incident, and he was discharged at the end of three weeks. He has been examined often since then, and has at no time shown any remaining evidence of the injury.

The course of events in this case left me at a loss for an accurate explanation, when the need for proper diagnosis arose. At my first examination, the child presented an almost classic picture of a patient with compression of the brain from an extradural hemorrhage, but it did not seem reasonable to hold to this diagnosis in view of the rapid and complete clearing up of signs and symptoms without operative relief. It was evident that there had not been time for the absorption of an extradural hematoma or of a subdural collection of blood causing the same sort of local pressure. The possibility

that the sudden relief of symptoms was due to the spreading into a thin layer of a previously localized blood mass in either the extradural or the subdural space was considered, but this seemed to be quite unlikely without some residual effect. Local contusion of the cortex, with its associated actual tissue damage, could have accounted for the signs of motor and reflex involvement, but here again, the recovery came too soon. An acute focal edema of the brain, bringing about the same sort of local ischemia as that caused by an extradural hematoma, could have caused the conditions present when the boy was admitted, it could have been resolved quickly enough to allow the speed of improvement shown, and it could quite properly have been expected to clear up without permanent brain damage. As there seemed to be no better explanation, this was accepted as a working diagnosis, and further examples were sought for, in the hope of proving or disproving the actual existence of such a focal edema.

This occurrence of clinical findings strongly suggesting extradural bleeding but apparently due to some other condition has been noted in the writings of others interested in this subject. The only actual case reports that I have found so far were published by Boston observers some fifty years ago. The first one, by Walton and Brooks,¹ gives the history of a young woman who was thrown from a horse, struck her head violently against a rail, and developed signs suggesting middle meningeal hemorrhage. At operation, neither extradural nor subdural bleeding was found, but on opening the dura the surgeon released about half an ounce of clear serum, and believed that the brain was edematous but otherwise normal. The patient improved slightly for a time, but then became worse and died. Post-mortem examination showed a few small areas of deep hemorrhage, none of which explained the unilateral paralysis, and the authors concluded that this had been caused by local edema. In the course of their discussion they said

It is not uncommon in children to find local paralysis following blows upon the head, closely simulating the results of hemorrhage, but completely disappearing in the course of a week or two, a fact which has to be borne in mind in making the diagnosis of middle meningeal hemorrhage in early life. The case here reported, together with others which have been called to our attention, would seem to indicate that similar conditions may obtain in adult life. Whether this pathology is accepted or not, the practical bearing of such cases upon our experience is* to throw a certain weight in favor of conservatism in doubtful cases, though by no means lessening the demand for operation in the typical case.

The second patient, reported by Walton,² was a six-year-old boy who was struck by a bicycle and

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From the Department of Neurosurgery, Rhode Island Hospital.
†Surgeon in-chief, Department of Neurosurgery, Rhode Island Hospital.

was dazed but not made unconscious. Later, he had some fever and vomited. He was fairly well until twenty-four hours later, when he became first drowsy and then unconscious, with paralysis of the right arm, leg and face. The right pupil was larger than the left, but reacted to light, there was incontinence of urine and feces, and pressure on a contusion behind the left ear caused crying. Nine hours later he was partially conscious and was regaining the use of the paralyzed muscles, so that operation was delayed. Six days after the accident he was completely well, except for a complicating sore throat, which was considered to be a coincidence. The third report, also by Walton,² concerned a three-and-a-half-year-old girl who was thrown to the floor from a small swing and struck her head. She was dazed, and later vomited. On the following day she had paralysis of the left arm, and exploration of the head was advised. Overcrowding of the hospital caused a delay of twelve hours, by which time she seemed much better and was beginning to use the left hand, so that no operation was done. Her convalescence was rapid, and she made a quick and complete recovery, being entirely well when seen two years later. Walton regards these patients as having had subarachnoid serous exudation and says

That a more or less diffuse oedema, whether involving the subarachnoid cavity or the brain itself, or both, and whether accompanied or not by marked laceration, may play a part in prolonging the general symptoms of concussion, seems a not improbable supposition, it is not, however, of this class of cases that I would speak at length, but rather of those cases in which a local paralysis of more or less temporary nature accompanies such general symptoms, the pathology being here, I apprehend, a local accumulation of fluid under the arachnoid resulting from rapid exudation at the point of most marked bruising, whether the result of direct violence or of contrecoup. For the unilateral paralysis there seems absolutely no plausible explanation, except the pressure of the fluid, and the relief of paralysis was apparently due to relief of this pressure. This lesion is to be particularly borne in mind in the case of children and young adults, and perhaps in alcoholic patients. In elderly patients the same set of symptoms points more decidedly toward hemorrhage.

Cushing³ discusses the physiologic effects of acute compression and states

We must continually bear in mind the difference between a local and a general increase in tension. Inasmuch as the pressure effects of a local process are greater in its immediate neighborhood than at a distance, and inasmuch also as there is considerable pressure discontinuity between the three intracranial compartments, owing to the fairly rigid partitions formed by the falx and tentorium cerebelli, a local pressure, let us say over one hemisphere, may exceed the local arterial pressure and lead to a local anemia sufficient to throw the adjoining parts of the brain out of function without seriously affecting the other hemisphere or the subtentorial structures, of which the medulla is of prime importance.

And in considering extradural and subdural hemorrhage, he says "Confusion may arise in certain cases, owing to the fact that acute, traumatic cerebral edema may closely simulate the general pressure phenomena which accompany actual extravasations of blood."

Current authorities on head injuries recognize the existence of states imitating extradural bleeding, but do not lay great stress upon them. Munro^{5, 6} remarks

In children, hemiplegia and convulsions commonly occur in uncomplicated cerebral oedema. There appears to be a type of malignant and sometimes strictly localized oedema of the brain that will present expansile characteristics. I have usually seen it develop as a postoperative complication.

Rowbotham⁷ believes that interval hemiplegias may be caused by edema, among other conditions. Brock⁸ writes "For rare instances of so-called malignant edema which develop rapidly and do not respond to ordinary methods of dehydration and repeated lumbar puncture, exploratory trephine will have to be resorted to, to rule out meningeal hemorrhage." Gross and Ehrlich⁹ deny the existence of a process such as that assumed above and say

Focal edema of the brain with the development of localizing signs and symptoms which simulate a middle meningeal hemorrhage, has been postulated by numerous observers. This has been used to justify exploration when middle meningeal hemorrhage has been sought and not found, and yet recovery has ensued. It is possible that an extradural clot may be confined over the occipital or occipito-parietal area, more rarely its situation may be far anterior. The improvement following negative exploration can probably be attributed to the decompressive effects concomitant with opening of the dura mater. This serves to prevent fatal cerebral compression. With the tiding over of the critical period, life is sustained, and as the epidural clot slowly reabsorbs, recovery takes place.

At the Rhode Island Hospital, during the past five years, we have treated a total of 8 patients on whom we made the diagnosis of acute focal edema of the brain. The ages varied from ten months to eleven years, we have seen no clear-cut case in an adult. In the same period we have had over 500 children with head injuries, so that the incidence in our experience is low, being well under 2 per cent. Seven of these children were boys. In most cases the child fell and struck his head on the floor or the ground. Linear fracture of the vault, without depression, was present in 3 cases, in 1 of which there was an additional fracture of the maxilla. There was initial unconsciousness in 3 patients. The interval between the injury and the onset of focal signs varied from fifteen minutes to six hours. The focal signs included one-sided reflex changes indicating cortical involvement, Jacksonian convulsive movements and in 1 patient a combination of Jacksonian and generalized convulsions, and one-sided paralyses of varying degrees. Traumatic shock was present in only 2 patients.

It is our practice not to do a lumbar puncture in the presence of shock or when acute extradural or subdural bleeding is suspected, for fear of lessening intracranial pressure and thus increasing bleeding, for these reasons, the cerebrospinal-fluid findings during the active phase of this condition are not available. Punctures done during

or soon after the subsidence of the acute symptoms, however, have shown normal pressures, normal protein levels and the absence of red blood cells in most cases, in 2 patients, the fluid has shown a few red cells, and in 1 it has shown a slight rise in the amount of protein relative to the age, being 36 mg per 100 cc in a boy of eleven years. The time needed for the complete disappearance of clinical evidence of the condition has varied from three to twenty-four hours.

We had thus gone along for five years, making this tentative diagnosis as a logical necessity but without actual proof of its existence, until May 1, 1948, when a four-year-old girl was admitted to the hospital. An hour earlier, she had been knocked down by a bicycle and had struck her head on the sidewalk. She became unconscious at once and was carried into the house, where she regained consciousness in a few minutes and vomited. Fifteen minutes later she again lapsed into unconsciousness and began to have convulsive movements of both arms and legs, the left arm and leg being definitely more involved than the right. On admission she was completely comatose, with no apparent response to any stimulus, and had occasional spontaneous movements of the right arm and leg, with no movement at all of the left arm and leg. There were contusion and hematoma of the scalp in the right temporal region and some bleeding from the right ear. Her pupils were moderately dilated, equal and regular, with good reaction to light, and there was a tendency to left-sided deviation of the eyes associated with deviation of the head to the left. The other cranial-nerve functions were grossly normal. The reflexes were overactive on both sides, and there was a questionable Babinski response on the right. The pulse was rapid and of fair quality, and the systolic blood pressure was 130, with no readable diastolic pressure. Breathing was deep and labored and within a few minutes stopped altogether. Artificial respiration was started, and she was given oxygen. We believed that she had a probable compound basal fracture on the right, with some brain contusion, and extradural hemorrhage on the right side. The outlook regarding recovery seemed to be very poor. She was taken at once to the operating room, and a right subtemporal exploration was made without anesthesia. The usual incision emptied out a large scalp hematoma, and showed moderate contusion of the temporal muscle but no apparent fracture line. Removal of the bone showed no extradural bleeding or clot. The underlying dura mater was tense, and there was a slight, bluish discoloration. No free blood or clot was found when the dura was opened. The underlying brain was swollen and edematous, and there were no pulsations to be seen. The dura was opened widely, and the subdural space was explored carefully with a flat, narrow brain retractor so that an area about 10 cm in diameter was investigated, but no blood or clot was found, and there was no apparent

hygroma. After these procedures, the brain seemed to be much less swollen and edematous, and it resumed its normal pulsations. Soon after the dura was opened the child began to breathe of her own accord. The dura was left open, and the wound was closed in the usual way. Within a few hours the girl was fully conscious, oriented, co-operative and apparently well. The positive Babinski response persisted for about twenty-four hours, but after that time no neurologic abnormality could be made out. X-ray films of the skull showed a linear fracture of the frontal bone and the temporal defect left by the operation, no fracture was evident in the cervical spine. A lumbar puncture was done on the fourth day, with entirely normal findings. During her hospital stay the youngster had no remaining evidence of brain damage and was bright and happy. She was discharged on the eighteenth day and has stayed well since that time.

I cannot believe that an extradural clot not found at operation, and lying either well in front of or behind the area explored, as suggested by Gross and Ehrlich,⁹ could account for the focal signs shown by this patient, nor can I believe that, with complete recovery within a few hours, there was time for the removal of such a clot by the slow absorption described by them.

The following account, then, probably best explains the pathologic conditions present in this patient. The loss of consciousness coming on at the time of the injury was due to brain concussion, the exact nature of which has not, as yet, been satisfactorily determined. The child recovered from this and then developed signs of compression of the motor cortex characteristic of a rapidly expanding lesion. The three stages of physical compensation, venous congestion and capillary anemia, so well described by Trotter,¹⁰ came on in quick succession. The compression then spread more widely and involved the medullary centers. Swelling and edema of the brain, sufficient to account for capillary anemia, were actually seen in an area where lack of blood supply would cause the focal signs that had been noted. When the pressure was relieved, the vital centers regained their normal functions almost at once, the edema of the brain was seen to subside, and the signs of cortical ischemia were lost in a few hours. It is probable that a process such as this can only be shown in the operating room, even if there should be opportunity for post-mortem examination, it seems unlikely that the condition would last long enough to be evident to the pathologist. I believe that the findings in this last patient indicate the actual occurrence of acute focal edema of the brain.

SUMMARY

Observations made on a series of 7 children, having signs and symptoms strongly suggesting those caused by extradural hemorrhage, but with such rapid and complete recovery without operation as

to cast doubt on this diagnosis, are reported. With particular reference to the time elements present, consideration of various pathologic processes that might be expected to bring about such a clinical picture leads to the conclusion that acute cortical edema, with associated capillary anemia, best explains the condition. This view is supported by the reports and comments of other writers. The finding of visible edema in the region of the motor cortex at operation on an eighth child is reported, and it is believed that this confirms the explanation previously made. In my opinion, acute focal edema of the brain can occur in children with head injuries, and I regard it as a recognizable clinical entity.

184 Waterman Street

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EXTRARENAL AZOTEMIA

Report of a Severe Case with Recovery

CHARLES F APPEL, M D,* AND JAMES H TOWNSEND, M D†

CAMBRIDGE, MASSACHUSETTS

AS FAR back as 1912 From and Marie¹ reported the occurrence of prerenal azotemia in cholera-form enteritis. Similar observations of prerenal azotemia were made by Nobécourt, Bidot and Maillet² in gastrointestinal disturbances in infancy in 1912 and by Tileston and Comfort³ in intestinal obstruction with vomiting in 1914. Only in recent years, however, has this condition been more completely understood.

The characteristic picture of extrarenal azotemia is that of renal failure without actual renal disease or of renal disease not sufficient to explain the signs of renal failure present. The more important signs of extrarenal azotemia include an elevation of the nonprotein nitrogen of the blood, uremic odor of the breath, dehydration, loss of electrolyte (particularly the chloride ion), and oliguria or anuria. The eye-grounds, on the other hand, appear normal, the blood pressure is not elevated, and the specific gravity of the urine is not markedly diminished, if at all lowered. Casts, red cells and white cells may be present in the urine, but these characteristically disappear.

The conditions in which extrarenal azotemia may occur are numerous, the following being mentioned by Jeghers and Bakst⁴: coronary thrombosis, alkalosis, pyloric obstruction, peritonitis, liver-kidney syndrome, yellow fever, gastrointestinal hemorrhage, postoperative complications, congestive heart failure, reaction to transfusion and intravenous therapy, Weil's disease, Addison's disease, pneumonia, allergy, diabetes mellitus, shock, acute

pancreatitis, diarrheal disease, heat cramps, drug intoxication, and burns.

In 1941 Garis⁵ reported a case of prerenal uremia due to papilloma of the rectum. In the same year Layne and Moir⁶ reported several cases of extrarenal uremia, an unusual one being a case of tabetic crisis with persistent vomiting. O'Donovan,⁷ in 1944, described 2 cases of extrarenal azotemia resulting from pyloric obstruction.

It is believed that the elevation of the nonprotein nitrogen of the blood in prerenal azotemia originates from one or both of two sources: an impaired elimination of the nonprotein nitrogenous products of the blood, or an increased production of these products. Jeghers and Bakst⁴ described the following basic causes of extrarenal azotemia: a drop in blood pressure, hypochloremia and hyponatremia, dehydration, liver damage, and protein catabolism. All factors need not be present in the same patient, but sometimes a combination of conditions or even a single one is sufficient to produce prerenal azotemia.

Fishberg⁸ considers a similar group of factors: hypochloremia, low arterial pressure, toxic nephritis, and alkalosis. Furthermore, Fishberg believes that the primary pathogenic factor in most — if not all — cases of prerenal azotemia with impaired renal function is a diminution of blood flow through the kidneys. This appears to be true of the causes enumerated by Jeghers and Bakst.⁴

A drop in systemic blood pressure reduces the blood flow through the glomeruli, diminishes the urine volume and, if of sufficient magnitude, results in azotemia. Hypochloremia and hyponatremia

*Resident in medicine Mt. Auburn Hospital.

†Chief Medical Services Mt. Auburn Hospital.

are generally related to excessive loss of fluid (as in persistent vomiting, diarrhea or perspiration). With the resultant dehydration, there is a diminished blood volume, hemoconcentration, reduced blood flow through the glomeruli, and impaired glomerular filtration.

According to Jeghers and Bakst,⁴ patients with azotemia and liver damage have had inadequate study for hypochloremia, hyponatremia and low blood pressure to determine whether liver damage per se produces azotemia.

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lytic therapy is difficult to explain on this basis. Alkalosis is frequently associated with vomiting, and in those cases the mechanism could be explained by dehydration.

The common denominator, then, in the pathogenesis of prerenal azotemia appears to be diminished blood flow through the kidneys, which fortunately is reversible in many cases, provided treatment is started early. On the other hand, if treatment is instituted too late or is inadequate, irreversible renal damage may occur.

In the following case the signs of severe renal failure were caused by the mechanism described

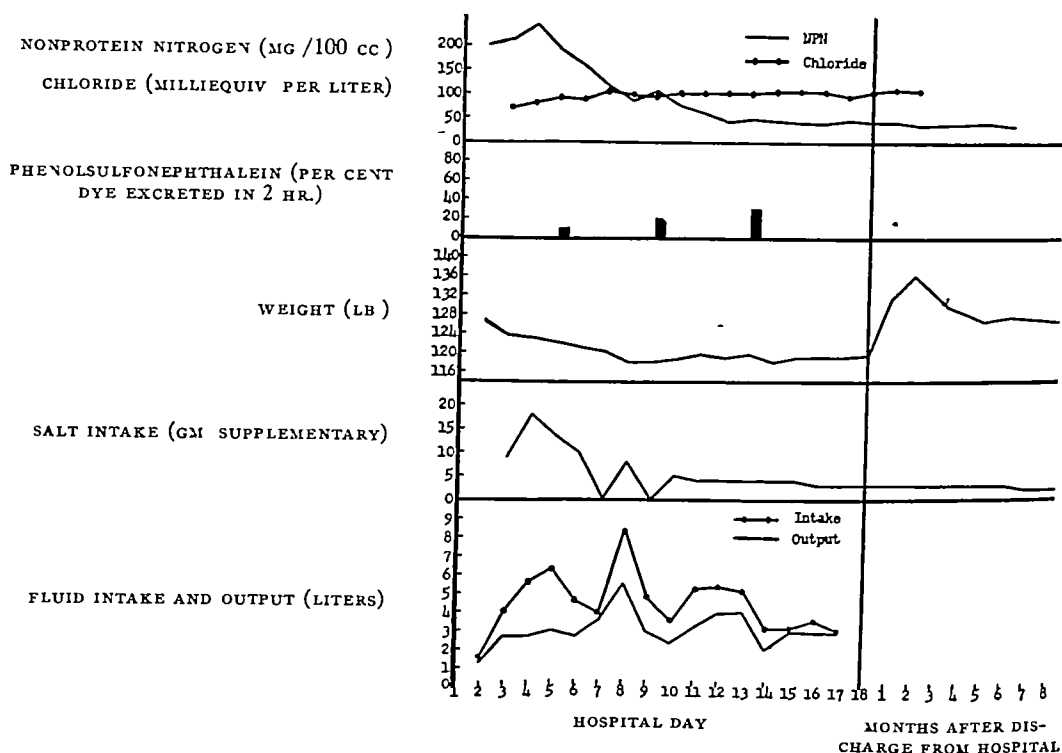


FIGURE 1 Course of the Blood Nonprotein Nitrogen and Chloride, Phenolsulfonephthalein Excretion Test, Body Weight, Supplementary Salt Intake and Fluid Intake and Output in the Hospital and during the Eight Months' Follow-up Period.

if there is associated impaired function. He cites the example of urea given to a patient with normal kidneys in amounts exceeding that of accelerated protein catabolism without producing an increase in urea of the blood. His final conclusion is that "when considerable azotemia is present renal excretion is subnormal."

In the review of the factors enumerated by Fishberg⁸ presented above, hypochloremia and low arterial pressure were discussed. The conception of toxic nephritis is a hypothetical one. Damage to the kidneys, as through acute infections, is supposed to occur by circulating toxins in the blood. These have not been demonstrated, and, furthermore, the response to hydrotherapy and electro-

above. After intensive therapy the renal function returned to normal.

CASE REPORT

J. D., a 37-year-old rubber-factory worker, was admitted to the hospital on January 26, 1947, with the chief complaint of abdominal pain of 15 days' duration. While he was at work on the night shift in the hot and moist environment of a rubber factory, severe frontal headaches followed by a chilliness and continuous anorexia, and nausea without abdominal pain developed. He continued to work, but on the following morning he vomited material that was not grossly bloody. Shortly afterward a sharp pain appeared in the lower abdomen near the midline, shifting at times to the epigastrium but with no relation to meals. There was also inconstant and transient pain in the lumbar region, radiating anteriorly to the lower abdomen. The patient remained in bed at home, but his condition became worse. The abdominal pain became more severe, and the nausea, vomiting and headache persisted unabatingly. Eight days before admission the patient summoned his family physician,

who believed he had a peptic ulcer and prescribed a regime of milk, cream and "amphojel." Nevertheless, the symptoms continued, so that hospitalization was finally recommended. There was no history of hematemesis, jaundice, melena, clay-colored stools, constipation or diarrhea.

The patient had noted bleeding from the gums for the past week, and on the day of admission, he had an episode of epistaxis, which stopped spontaneously. Although there was no history of dysuria or hematuria, he had usually drunk about 3 quarts of water while at work for the past 1½ years. However, his fluid intake was markedly reduced after the onset of the vomiting. Furthermore, according to the patient's wife, severe oliguria had begun 10 days before admission, but the exact degree of the oliguria could not be ascertained.

The past history gave no evidence of cardiac or renal disease, scarlet fever or frequent sore throats.

Physical examination revealed a fairly well nourished and well developed man, moderately dehydrated and drowsy, lying flat in bed without dyspnea or cyanosis and not answering questions readily. There was a pterygium of the left eye and a subconjunctival hemorrhage below the right iris. Fundoscopic examination disclosed no choking of the disks and no hemorrhage, exudate or spasm of the arteries. There were dried blood clots in the right naris, and generalized gingival bleeding, with reddish discoloration of the tongue. No abnormal findings were present in the chest. The blood pressure was 144/90. On deep palpation there was slight tenderness in the epigastrium and moderate tenderness at both costovertebral-angle areas. Rectal examination revealed no abnormal masses. Although the gloved finger showed no evidence of gross blood, the specimen yielded a ++ guaiac test for occult blood.

The initial impression was that the patient had a bleeding peptic ulcer and possibly a vitamin C deficiency, or some form of blood dyscrasia. Therefore, he was placed on a regimen of Meulengracht diet, "gelusil," tincture of belladonna and large doses of vitamins.

On the 2nd hospital day the patient continued to be drowsy and to complain of pain in the lumbar region, radiating to the lower abdomen. The prothrombin time was 16 seconds (normal, 17 to 22 seconds), the bleeding time was 2 minutes and 7 seconds, and the clotting time, 4 minutes and 1 second. The red-cell count was 5,050,000, with a hemoglobin of 15 gm, and the white-cell count 11,300, with a normal differential count. The blood nonprotein nitrogen was 200 mg per 100 cc. Urinalysis showed a trace of albumin with 8 to 10 white cells and 30 to 40 red cells per high-power field in the sediment. In view of the clinical picture and laboratory findings, the plan of treatment was changed to increase substantially the daily fluid and electrolyte intake.

Figure 1 demonstrates the hospital course, showing how the blood nonprotein nitrogen rose to 245 mg per 100 cc and then fell gradually to normal, remaining so. The fluid intake was entirely by mouth except on the 3rd hospital day, when 1000 cc of 5 per cent glucose in physiologic saline solution and 1500 cc of 5 per cent glucose in distilled water was given intravenously. The carbon dioxide combining power fell from 32.6 milliequiv on the 3rd hospital day to 23.0 milliequiv per liter (normal, 23 to 30 milliequiv) on the 8th hospital day. Subsequent urinalyses showed specific gravities in the realm of 1.010 with traces of albumin, a few white and red cells and occasional granular casts. The blood pressure remained constant at about 134/84 throughout the hospital course.

An electrocardiogram on the 4th hospital day showed a sinus bradycardia at a rate of 50 per minute, with left-axis deviation, but a second tracing 13 days later was entirely normal. On the 5th hospital day the serum protein was reported as 7.2 gm, the albumin as 4.6 gm, and the globulin as 2.7 gm per 100 cc, with an albumin-globulin ratio of 1.8. A barium enema on the 7th hospital day showed the barium to pass freely to the cecum. There was no evidence of carcinoma or diverticulitis. A chest x-ray film disclosed no abnormalities of the heart or lungs. On the same day a stool examination demonstrated no ova, parasites or blood. By the 9th hospital day the patient had become stronger, with improved appetite, so that he was allowed to be ambulatory. An intravenous pyelogram on the 12th hospital day showed normal-appearing calyces, pelves and ureters and normal excretory function. The blood phosphorus was reported as 4.1 mg per 100 cc on the 16th hospital day, and an upper gastrointestinal series was entirely normal.

The patient was discharged on the 18th hospital day on a regime of supplementary salt of 4 gm and 10 glasses of water a day. His follow-up course in the outpatient department was uneventful (Fig 1). Urinalyses done 2, 4 and 6 months after discharge revealed clear urine with specific gravities of 1.025, 1.020 and 1.018 respectively.

DISCUSSION

The unusual feature of this case was the extremely high nonprotein nitrogen that fell from 200 to 42.5 mg per 100 cc after ten days of intensive electrolytic therapy and hydrotherapy. At no time during this treatment could the output be considered low. The significance of alkalosis could not be ascertained altogether. While the patient was in the hospital, alkalosis was never more than slight. Its magnitude before admission, on the other hand, might have been more marked, but unfortunately was not known. The blood pressure remained constant around 134 systolic, 84 diastolic. It never reached the low levels of traumatic shock or severe transfusion reaction.¹⁰ The return of renal function to normal was shown by an excretion of 60 per cent of phenolsulfonephthalein in two hours (compared with 20 per cent excretion of the dye eight days previously) and by the normal excretion of dye in the intravenous pyelogram four weeks after the onset of the illness. Furthermore, the sustained normal nonprotein nitrogen and the specific gravity of 1.025 and 1.020 two and four months after the onset of illness helped to substantiate the return of renal function to normal.

The rationale in therapy was to restore the continued loss of fluids and electrolytes as soon as possible by the increased fluid and sodium chloride intake by mouth and by infusions of glucose and physiologic saline solution intravenously. In this way hemoconcentration and dehydration were reduced, blood flow through the glomeruli increased and normal renal excretion restored.

SUMMARY

The occurrence and pathogenesis of extrarenal azotemia are discussed.

A case of severe prerenal azotemia preceded by dehydration and moderate intake of alkalis, and followed by return of renal function to normal after intensive electrolytic treatment and hydrotherapy, is presented.

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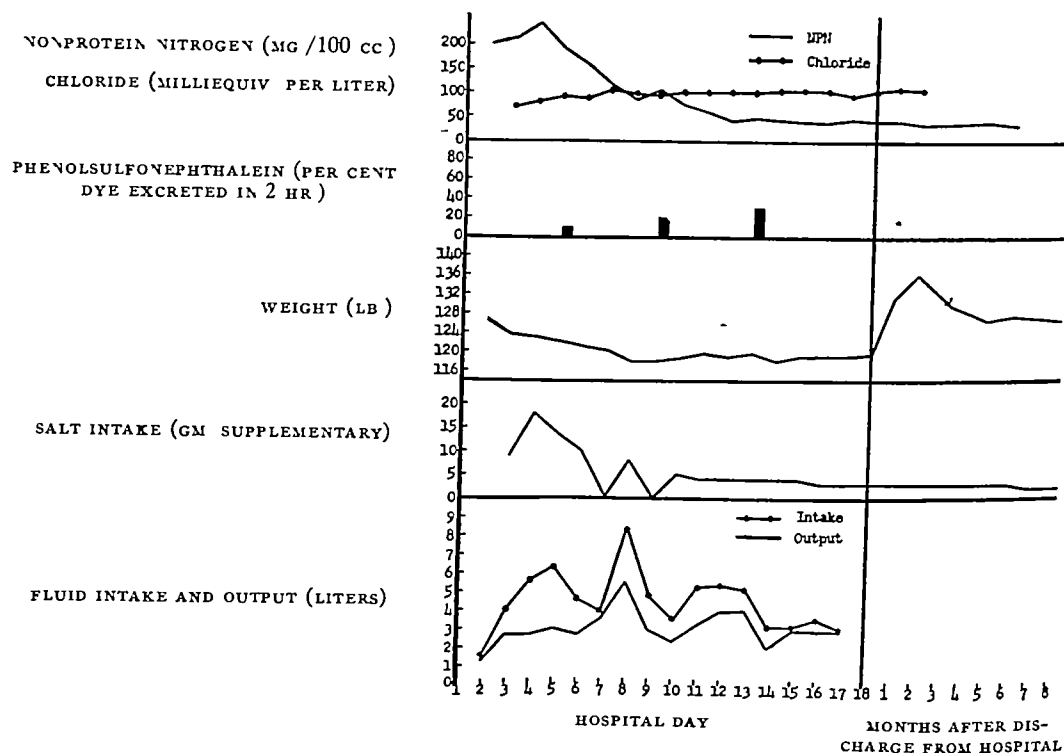


FIGURE 1 Course of the Blood Nonprotein Nitrogen and Chloride, Phenolsulfonephthalein Excretion Test, Body Weight, Supplementary Salt Intake and Fluid Intake and Output in the Hospital and during the Eight Months' Follow-up Period

if there is associated impaired function. He cites the example of urea given to a patient with normal kidneys in amounts exceeding that of accelerated protein catabolism without producing an increase in urea of the blood. His final conclusion is that "when considerable azotemia is present renal excretion is subnormal."

In the review of the factors enumerated by Fishberg⁸ presented above, hypochloremia and low arterial pressure were discussed. The conception of toxic nephritis is a hypothetical one. Damage to the kidneys, as through acute infections, is supposed to occur by circulating toxins in the blood. These have not been demonstrated, and, furthermore, the response to hydrotherapy and electro-

above. After intensive therapy the renal function returned to normal.

CASE REPORT

J. D., a 37-year-old rubber-factory worker, was admitted to the hospital on January 26, 1947, with the chief complaint of abdominal pain of 15 days' duration. While he was at work on the night shift in the hot and moist environment of a rubber factory, severe frontal headaches followed by a chilliness and continuous anorexia, and nausea without abdominal pain developed. He continued to work, but on the following morning he vomited material that was not grossly bloody. Shortly afterward a sharp pain appeared in the lower abdomen near the midline, shifting at times to the epigastrium but with no relation to meals. There was also inconstant and transient pain in the lumbar region, radiating anteriorly to the lower abdomen. The patient remained in bed at home, but his condition became worse. The abdominal pain became more severe, and the nausea, vomiting and headache persisted unabatingly. Eight days before admission the patient summoned his family physician,

in whatever tissues it might be found. The fourth was to apply the agent in controlled clinical studies and to evaluate by sound statistical methods the results of therapy.

What has thus far been said applies to all chemotherapy. The following sections review recent advances in understanding and employment of chemotherapy directed in particular against bacterial infections. The four steps outlined above serve as framework for the discussion of chemotherapeutics in general use, after which some that are presently in the developmental stage are briefly reviewed.

IN VITRO STUDIES AND MECHANISM OF ACTION

Prior to 1935 a great number of inorganic and organic substances were known to inhibit the growth of micro-organisms or to kill them. Metallic ions, phenols, aliphatic alcohols, organic acids, dyes, oxidizing agents, soaps and detergents are classes of compounds displaying an antiseptic or, at higher concentrations, a disinfectant action. These agents vary considerably in specificity for different organisms, the gram-positive group being, in general, most readily attacked. Logarithmic killing curves are obtained with adequate concentrations, and the death rate is critically related to concentration. The deficiency of all these substances lies in their indiscriminate affinity for a multitude of host proteins along with those of pathogenic organisms, a circumstance that led to the vague and inexact descriptive term "general protoplasmic poisons." Their unfavorable chemotherapeutic ratio restricts their use (with the exception of a few dyes and organic acids) to topical applications and sterilization of inanimate objects.

Sulfonamides

Domagk's introduction of prontosil⁸ and the subsequent use of the sulfonamides (Fig. 1) was remarkable not because this class of compound was more potent than the antiseptics in inhibiting bacterial growth. On the contrary, comparable concentrations of phenolic compounds and mercuric chloride accomplish the same end-result, whereas the newer cationic detergents are effective at less than 0.5 mg per 100 cc.⁹⁻¹² The remarkable fact was that the effective sulfonamide concentrations should be tolerated, in body fluids without prohibitive toxicity. Thus was the era of systemic antibacterial chemotherapy inaugurated.

The sulfonamides are often stated to be purely bacteriostatic. There is clear evidence, however, that although low concentrations inhibit growth, higher concentrations cause a progressive reduction in the viable count.¹⁴ The bacteriostatic effect is not immediate in onset but occurs only after several cell divisions in the presence of the drug. If nongrowing organisms are suspended in a sulfonamide solution and then removed and placed in a normal growth medium the drug is without effect.¹⁵

The bactericidal action likewise appears only in a medium favoring growth. The respiration of nongrowing cells is not affected,¹⁶⁻¹⁷ but the additional respiration entailed in growth is inhibited.¹⁶⁻¹⁸ The suggestion that bacteriostasis is secondary to this inhibition of respiration is neither more nor less valid than the view that the latter is the result of the former.

The inactivity of the sulfonamides in the presence of pus and tissue extracts soon led to the isolation of para-amino-benzoic acid (PABA), which competitively antagonizes sulfonamide action.¹⁹⁻²⁰ The idea that these drugs blocked the normal bacterial

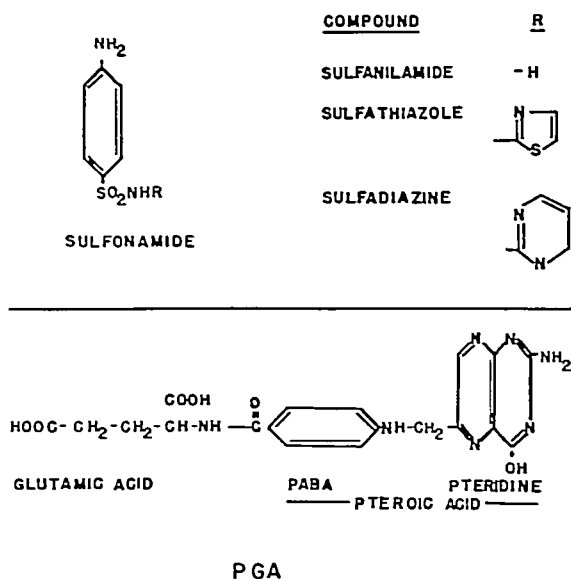


FIGURE 1 Structural Formulas of Some Sulfonamides and Pteroylglutamic Acid (Folic Acid)

utilization of PABA¹⁵ gave impetus, through the Woods-Fildes theory¹⁹⁻²¹⁻²² to the whole fruitful study of biologic antagonisms.²³⁻²⁴ It was finally confirmed by the discovery of folic acid²⁵ (pteroylglutamic acid, PGA) as an essential substrate in the growth of many bacteria. This compound (Fig. 1) is a conjugated molecule containing one residue each of glutamic acid, PABA and a base (pteridine). That sulfonamides prevent the incorporation of PABA into the PGA molecule now seems established beyond reasonable doubt. Organisms that are entirely independent of the need for PGA are not sensitive to sulfonamides. Organisms that require *ready-made* PGA as a "growth factor" are also insensitive to sulfonamides, since they lack the metabolic step upon which the drug acts²⁶; PGA analogues, however, inhibit their growth.²⁷⁻²⁸ Sulfonamide-sensitive organisms are evidently those that must form their own PGA from PABA. Sulfonamide growth inhibition in such organisms is relieved *either* by PABA *or* by PGA.

MEDICAL PROGRESS

ANTIBACTERIAL CHEMOTHERAPY*

AVRAM GOLDSTEIN, M D †

BOSTON

IT IS an interesting commentary on one man's impact upon the growth of scientific medicine that a review of a rapidly expanding field, written thirty-five years after his death, should comprise a mere addition of details to the broad guiding principles he established. In this thirteenth year of the clinical use of sulfonamides, the seventh of penicillin and the fourth of streptomycin, it seems entirely appropriate to introduce the discussion by a restatement of the fundamentals upon which Ehrlich¹⁻³ founded the science of chemotherapy.

As intended by its author, the word "chemotherapy" means the treatment of parasitic disease by direct chemical attack upon invading organisms—viruses, fungi, bacteria, spirochetes, protozoa or helminths. In my opinion extending this meaning to include the treatment of a variety of pathologic states (for example, "chemotherapy of heart disease") blurs a distinction that is as fundamental today as when it was first introduced by Ehrlich. It is precisely the killing of pathogenic forms of life with a *minimum* of effect upon the tissues and physiologic processes of the host that is the unique goal of chemotherapy. All drugs that may be employed to this end are referred to below as "chemotherapeutics,"† arbitrary distinctions between molecules produced in the laboratory and those (the so-called antibiotics⁶) whose synthesis the organic chemist has not yet achieved being avoided.

Chemotherapeutics do not act primarily upon the host but rather combine chemically with certain systems of parasitic organisms. Ehrlich showed that affinity for a parasite often requires a very exact structure in a drug, whose entire potency may hang upon addition or removal of a single atom. He summarized the high degree of specificity of this combination in his well known "receptor" or "side-chain" hypothesis.⁷ From the concept that chemotherapeutic action is fundamentally a chemical combination came two important corollaries: that the basic phenomena should be amenable to study in the isolated parasite, in vitro, wherever the organism could be grown, and that stoichiometry or mass law relations, or both, must apply as in

any chemical reaction—that is, for a given system a definite total dosage or concentration, or both, will be required for complete combination with the organisms.

Ehrlich early realized that although a great many drugs were effective at some concentration in vitro, toxicity for the host might prevent their systemic utilization. When he had shown, however, that affinity for parasite (parasitotropism) and for host tissues (organotropism) by no means went hand in hand, the way was opened for molecular modifications that would increase the former or decrease the latter affinity. Ehrlich's view that drugs also combined with tissue cells through receptor side chains was an adequate expression of the facts at a time when the specificity of protein interactions was still dimly understood. Today the same views could be reformulated in terms of enzyme-mediated steps in metabolic processes—some playing a role in both parasite and host, and others being unique to each organism or host tissue.

The practical implications of specific and differential toxicity to parasite and host were summarized in Ehrlich's *chemotherapeutic ratio*.¹ The criterion of usefulness of a chemotherapeutic is not in its absolute molar potency against the parasite but only in the *ratio* of dose first producing toxic effects in the host to that required to kill the parasite. *Comparisons between chemotherapeutics on a gravimetric basis are without significance in foretelling their possible clinical value.*

Thus, Ehrlich's work led to a clearly formulated approach to the development of agents useful in clinical chemotherapy. The first main step was to discover by isolation or synthesis compounds that would effectively kill the parasite at some reasonable concentration in vitro, and to study the mechanism of interference by such agents with the metabolic pathways. The second was to select drugs that would yield a satisfactory chemotherapeutic ratio—that is, agents sufficiently nontoxic to be of clinical promise—and to investigate the means of reducing toxicity, by modification of structure or otherwise. The third was to work out the practical pharmacodynamics—that is, the fate of the drug in the body—to determine the optimal dose, route and frequency of administration, and other special methods for bringing the drug into full chemical combination with the parasite,

*From the Department of Pharmacology, Harvard Medical School.

†Associate in pharmacology, Harvard Medical School.

‡The word appears in the designation of a Committee of the National Research Council⁴ during the war years and has been advocated more recently by Dr. B. D. Davis.⁵

at this task. The various penicillins* were shown to differ in the substituent acid coupled to the alanine amino-group.⁵¹⁻⁵² It was demonstrated that the type of penicillin produced varied with the substrate supplied — phenylacetic acid, for example, being coupled to yield benzyl penicillin. When isotopically labeled phenylacetylvaline was supplied, only the phenylacetyl portion was incorporated, demonstrating that the unique portion of the penicillin molecule is synthesized separately and coupled as a unit to any one of a number of organic acids.⁵³ The ring-condensed amino-acid portion can be synthesized, at least in part, from simple materials since labeled sulfur, supplied as sulfate, is recovered quantitatively in the penicillin molecule.⁵⁴

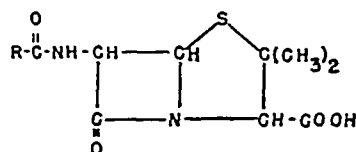
The penicillins are moderately strong acids whose sodium, potassium, calcium or other salts may be used therapeutically. The carboxyl group must be free and ionized, esterification destroying the entire activity of the molecule.⁵⁵ Two comprehensive reviews of penicillin chemistry have recently appeared.⁵⁶⁻⁵⁷

A remarkable preferential affinity for gram-positive organisms and spirochetes is shared by all the penicillins. That there are quantitative differences is established, p-hydroxybenzyl penicillin (X), for example, is more potent than benzyl penicillin (G) against most organisms.⁵⁸⁻⁶¹ But the general pattern of affinities is the same, and the differences have not appeared substantial enough to warrant large-scale commercial production of other types than penicillin G, which is now available in pure crystalline form, requires no refrigeration and is of standard potency.⁶² In accordance with established procedure the *unit* should long since have been dropped.

An interesting sidelight on the purification of penicillin is the finding by Hobby and her collaborators⁶⁴ that in some respects the protective action of crystalline benzyl penicillin is inferior to that of the cruder material in experimental animal infections. It has been suggested that the original mixture contained impurities of an antitoxic nature,⁶²⁻⁶⁴ that phenylacetic acid, which is known to potentiate penicillin action, was the responsible agent,⁶⁵ or that specific metabolic inhibitors were present.⁶⁶

Penicillin is bacteriostatic in threshold concentration and bactericidal in higher concentration.⁶⁷⁻⁶⁹ Neither effect is observed unless cells are growing,¹⁴⁻⁶⁷ and the killing action is most pronounced against young, rapidly growing organisms.¹⁴⁻⁷⁰ It is enhanced by substances and conditions that promote growth.⁷⁰ Cells exposed to penicillin show characteristic morphologic abnormalities, notably giant forms that fail to divide.¹⁴⁻⁷¹ It had been thought that the bactericidal effects of the drug resembled those of some of the common disinfectants.

But Eagle⁷²⁻⁷³ has recently shown, confirming earlier work by Hobby,⁶⁷ that the rate of killing does not follow increasing concentration beyond a certain point. Unlike disinfection, therefore, the bactericidal effect seems to depend upon the degree of blocking of a vital system whose complete saturation results in a constant maximal death rate. The onset of bacteriostasis is preceded by a short



PENICILLIN

TYPE	R
G	BENZYL $\text{C}_6\text{H}_5\text{CH}_2-$
X	P-HYDROXYBENZYL $\text{HO-C}_6\text{H}_4\text{CH}_2-$
F	PENTENYL $\text{CH}_3\text{CH}_2\text{CH}=\text{CHCH}_2-$
DIHYDRO-F	N-AMYL $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$
K	N-HEPTYL $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$

FIGURE 2 Structural Formulas of the Principal Naturally Occurring Penicillins

lag period,¹⁴ and a prolonged lag is observed before growth resumes when organisms are transferred to fresh medium after brief exposure to the drug.⁷⁴⁻⁷⁶ Respiration is not inhibited except under conditions favorable to growth.⁷⁷⁻⁷⁸ These findings are all so similar to those obtained with the sulfonamides that it is difficult to substantiate the earlier consensus that the action mechanisms of penicillin and the sulfonamides differed fundamentally from one another.

The ingenious studies of Pratt and Dufrenoy,⁶⁵⁻⁷⁹⁻⁸¹ who investigated the chemical reactivities of various portions of typical penicillin agar assay plates, showed that the drug promotes a shift of -SH to S-S and of aldehyde or enol to ketone, suggesting a primary interference with oxidation-reduction systems. These workers demonstrated that the zone of increased growth at the margin of an inhibition zone, corresponding to just subthreshold penicillin concentration, was the area in which the biochemical shifts described were most active. It is significant that by their methods the authors were unable to show any qualitative differences in the action of "sensitive" gram-positive and "insensitive" gram-negative organisms, provided only

*As is customary the word penicillin unless qualified is used here to denote penicillin G — benzyl penicillin.

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Dr. Robert H. Allen
U. S. A. Medical College

itself. As one might expect, the antagonism produced by the former is competitive, growth inhibition depending upon the ratio of PABA to sulfonamide. On the contrary, in the presence of PGA, sulfonamide is without effect, regardless of concentration, within limits. The antagonisms cited here have been demonstrated not only for bacteria but also for psittacosis virus, whose growth on embryonated eggs is inhibited by sulfonamides and restored by PABA or PGA.²⁹

This scheme explains the characteristic lag of several cell divisions before growth inhibition by sulfonamides occurs; it is assumed that PGA stores are being exhausted during this period, the synthesis of new PGA being blocked at once.²² The role of PGA in growth and metabolism, however, and in particular its curious connection with human erythropoiesis^{30, 31} are not understood. Furthermore, the relations may not be as simple as these generalizations indicate, since exceptions to the rules have been observed in certain organisms. It is also demonstrated that a number of compounds unrelated to PGA (methionine, xanthine and serine) are capable of antagonizing sulfonamide action noncompetitively, indicating that several enzymatically controlled steps may be successively inhibited by the drug.³²⁻³⁶ Moreover certain important respiratory enzymes are inhibited at reasonable sulfonamide concentrations.³⁷ The best summary of the evidence implicating systems other than the PABA → PGA reaction can be found in Henry's³⁸ review of five years ago.

Kumler and Daniels³⁹ attempted to explain the varying potencies of the different sulfonamides on the basis of resonance effects. Bell and Roblin⁴⁰ made a similar correlation between pK and potency, and made the interesting prediction that sulfadiazine (Fig 1) already possessed optimal antibacterial activity and could only be improved upon with respect to other pharmacologic properties (such as toxicity). This prediction was apparently correct. Of the newer systemic sulfonamides only sulfamerazine (monomethyl sulfadiazine) and sulfamethazine (dimethyl sulfadiazine) have merited widespread clinical trial, and neither is intrinsically more potent than sulfadiazine. Nor, in general, have various sulfonamides displayed appreciable differences in bacterial affinities (provided only that the para-amino group remain free), molecular changes in the N₁ substituent serving to modify quantitative rather than qualitative antibacterial properties.

Gramicidin, Tyrocidine and Tyrothricin

From a chronologic point of view the next potential chemotherapeutics to appear were tyrocidine and gramicidin, which Dubos⁴¹ obtained from *Bacillus brevis* by isolation from the crude mixture, tyrothricin. These compounds were shown to be bactericidal, preferentially against gram-positive

forms, and also to display a hemolytic action that, among other toxic features, prevented their systemic use.⁴² Gramicidin (or tyrothricin) is still employed to some extent in the treatment of surface infections caused by gram-positive cocci. Tyrocidine acts, in every respect, like a disinfectant, it markedly inhibits cell respiration and disrupts the bacterial cell wall. Gramicidin, on the other hand, inhibits growth, does not lyse bacteria and stimulates the oxygen uptake of nongrowing cells.⁴³ In view of these differences it is interesting that they should have become prototypes of the large group of substances now classed as "antibiotics"—a fine illustration of the fact that biologically produced antibacterials as a group have no unique mechanism of action.

Gramicidin and tyrocidine have proved unusually interesting from the structural standpoint. They are cyclic peptides containing a number of residues of various amino-acids, some being of the unusual d- configuration.⁴² Investigation by the newer techniques of counter-current distribution and paper chromatography has revealed at least four different gramicidins.⁴⁴ The major component contains l-tryptophane, d-leucine, d,l-valine, l-alanine, l-glycine and ethanolamine. The others differ in respect of one or more amino-acids. The minimal molecular weight appears to be approximately 8700, representing about 70 residues. Tyrocidine yields, on hydrolysis, ornithine, proline, valine, leucine, tryptophane, tyrosine, aspartic acid and glutamic acid of the usual configurations, and d-phenylalanine. Gramicidin-S consists of but five amino-acids, l-ornithine, proline, valine, leucine and d-phenylalanine.⁴⁵ As pointed out below, these unusual polypeptide arrangements prove to be typical of a number of naturally occurring antibacterial substances. The mechanisms whereby compounds of this type produce growth inhibition in one case and lyse a cell wall in another and the significance of the ever-present d-amino-acid, remain equally obscure.

Penicillins

The advent of penicillin^{46, 47} provided a clinical weapon of unsurpassed excellence not, again, because of its higher molar potency, but because its toxicity is negligible even at doses fantastically higher than those required for minimal antibacterial effect. The need to produce the drug biologically and in vast quantities to meet war requirements stimulated considerable research into its structure and the optimal conditions for its synthesis by the mold.⁴⁸ The first line of endeavor led to the surprising result⁴⁹ that the drug is (or appears to be) a curious ring condensation of two amino-acids—alanine and beta-dimethyl-cysteine (Fig 2). The structure was later confirmed by a token synthesis,⁵⁰ but the mold is still more efficient than the chemist.

drugs of this class the hydrolyzed residues display little if any of the original activity. The significance of the hexose and glucosamine components¹¹⁴ is not clear, nor the meaning of the similarity of the streptidine portion¹¹⁵ to the B vitamin inositol. From the observed increase in potency with pH it is inferred that the basic guanido groups of streptidine confer optimal properties in their uncharged state.

It has been observed¹¹⁶ that streptomycin can precipitate as a complex with desoxyribosenucleic acid (DNA), a fact that raised interesting possibilities in view of the intimate connection of the latter compound with protein-synthetic processes. Other investigators,¹¹⁷ however, showed that the complex actually dissociated at physiologic saline concentrations, that phosphate had opposite actions on the DNA-streptomycin complex and the antibacterial affinity of the drug, and that the enzyme desoxyribonuclease, which depolymerizes the complex, has no effect upon streptomycin potency. These facts call the significance of the action of the drug upon DNA into considerable question, the investigators also pointing out that viruses of the psittacosis-lymphogranuloma group, which are rich in DNA, are also relatively insensitive to streptomycin. Complex formation with ribonucleate has also been reported,¹¹⁸ and is discussed below.

Like penicillin, streptomycin is antagonized by a number of compounds. Anaerobic conditions or the presence of glucose reduces its potency but this is primarily the result of increased acidity.^{119, 120} Bivalent cations (magnesium, calcium and barium) and certain anions (phosphate, sulfate, citrate and tartrate) are competitive antagonists.¹¹⁷ Ascorbic acid and sulfhydryl compounds like cysteine and thioglycollate are also antagonists¹²⁰⁻¹²³, whether they act by lowering the redox potential of the medium is not clear, but such an interpretation would be consistent with the greater sensitivity of aerobic than anaerobic bacteria.^{124, 125}

Along these lines, Cavallito and his co-workers^{126, 127} have shown that penicillin, streptomycin and other complex antibacterial agents are capable of combining with certain thiols in isolated chemical systems. Whereas mercuric ion combines rather indiscriminately, penicillin and streptomycin are highly selective for -SH groups surrounded by proper reactive neighboring groups (for example, an amino-group separated from -SH by an exact number of carbon atoms). Once formed, the mercury complexes are readily reversed by other reactive thiols, but the penicillin and streptomycin complexes are not. The data are advanced in support of the view that combination with thiol groups mediates the antibacterial action of these drugs,^{125, 129} a suggestion that is consistent with the findings of Pratt and Dufrenoy. The interesting observation has been made¹³⁰ that penicillin can be considered a structural analogue of glutathione, whose function

is thought to involve maintenance of reduced sulfhydryl groups.

Fitzgerald and Bernheim^{131, 132} reported that the oxidation of benzoic acid by the tubercle bacillus is selectively inhibited by bacteriostatic concentrations of streptomycin and that this does not occur in resistant strains. Green, Iverson and Waksman¹³³ demonstrated interference by pyruvate or fumarate with streptomycin activity, an antagonism that is not shared by a number of other organic compounds. Rhymer et al.¹³⁴ showed that the structural analogue, lipositol, is a streptomycin antagonist. But none of these phenomena were shown to be related in a definite way to the action mechanism of the drug.

As Gaddum¹³⁵ has pointed out, there are two sharply defined categories of drug antagonism — one drug may compete with another for a receptor site, or one drug may form a chemical complex with another and thus prevent its combination (or if the affinity is great, remove it from combination). The PABA-sulfonamide antagonism is obviously of the first type and is thereby directly concerned with the drug's mechanism of action. A simple example of the second type is the neutralization of cationic by anionic detergents.¹³⁶ Antagonisms of this kind can give insight into the intimate manner of combination with cell receptors only by inference and deduction. Thus the demonstration that a sulfhydryl compound combines with a chemotherapeutic, or even reverses its action on the bacterial cell, suggests, *but does not prove*, that the drug acts by combining with bacterial -SH groups.¹³⁷ It must be concluded that, with the possible exception of the benzoic acid results, the work cited has yielded no proved antagonists of the first type. Consequently experiments with antagonists have as yet contributed little definitive information to knowledge of the sites and mechanisms of combination of penicillin and streptomycin with bacterial cells.

Mechanisms of Antibacterial Action

Broadly speaking, bacterial growth can be interrupted by interference with two main pathways: catabolic reactions yielding the energy required for protein synthesis, and the anabolic, synthetic processes themselves. To these should be added the special mechanisms that control cell fission and the reduplication of genetically functioning nucleoprotein.

The bacteriologic criterion of death is an irreversible inability to reproduce when the cell is introduced into fresh medium suitable for growth. It has proved difficult to make a sharp distinction between bacteriostatic and bactericidal action. If growth inhibition is prolonged, a logarithmic death phase sets in, indeed, a progressive loss of viability is observed even in a normal culture in the stationary phase, when growth has ceased.¹³⁸ The reproductive mechanism in bacteria appears

that a high enough penicillin concentration were used to inhibit growth of the latter. This points up the fact that sensitivity to most chemotherapeutics is relative, expressed in terms of a threshold concentration for growth inhibition.

One of the incidental findings in these experiments was the specific action of cobalt in enhancing penicillin activity *in vitro*⁸¹ and in experimental pneumococcal infection in mice.⁸² This may be another example of the penicillin-enhancing properties of substances that promote growth, in view of the recent report that vitamin B₁₂ is a cobalt complex.⁸³ Whether the curious phenomenon will prove clinically useful remains to be seen.

Penicillin at bacteriostatic concentrations inhibits ribonuclease,⁸⁴ mononucleotidase⁸⁵ and phosphatase⁸⁶ (not confirmed by a second group of in-

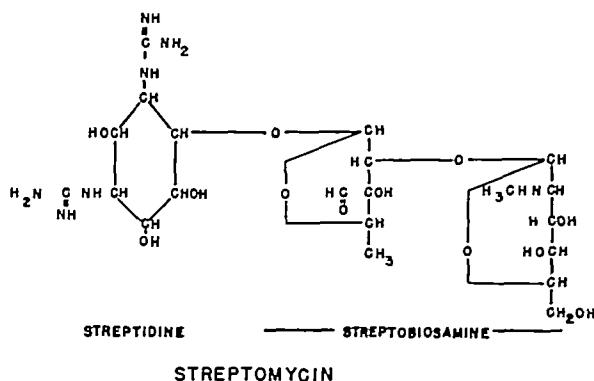


FIGURE 3 Structural Formula of Streptomycin

vestigators⁸⁷) Specific inhibition of other metabolically important enzymes has not been demonstrated.

Although a number of compounds are capable of antagonizing penicillin action,⁸⁸⁻⁸⁹ none have been shown to play a metabolic role analogous to that of PABA in the antagonism of sulfonamides. Penicillinase, an enzyme destroying the drug and produced by some bacteria,⁹⁰⁻⁹¹ is connected with one type of resistance (as mentioned below), and its elaboration by *Escherichia coli* probably explains the disappearance of a major portion of orally administered penicillin. But the enzyme clearly bears no relation to the fundamental action mechanism. Its incorporation into bacteriologic mediums to eliminate the penicillin present in body fluids taken for culture has become routine.⁹²

A remarkable series of studies by Gale and his collaborators⁹³ has revealed an entirely new and fascinating aspect of the problem of mechanism of action. They have shown that gram-positive but not gram-negative organisms are capable of actively taking up and concentrating free glutamic acid and lysine from the environment, and that this process is mediated by components of the cell

wall.⁹⁴⁻⁹⁵ The sharp distinction between the gram-positive and gram-negative groups is probably connected with the presence or absence of the magnesium-ribonucleate complex shown to be responsible for positive gram-staining properties.⁹⁴⁻⁹⁹ Penicillin acts upon the cell wall to prevent the amino-acid uptake, but only when the cells have grown in the presence of the drug. Penicillin is without effect upon the glutamic acid uptake of respiring, nongrowing cells.¹⁰⁰ Variants becoming resistant to penicillin have been shown to assume gram-negative properties,¹⁰¹⁻¹⁰² at the same time acquiring the ability to grow and reproduce without assimilating and concentrating glutamic acid, and thus, by an alternate metabolic pathway, becoming independent of the penicillin action. Indeed, it has been shown that such resistant forms are able, like most gram-negative organisms, to synthesize a number of amino acids.¹⁰²⁻¹⁰⁴

Tyrocidine, phenol and the detergents appear to act by a simple disruption of the cell wall¹⁰ (demonstrable in electron micrographs¹⁰⁵) so that glutamic acid and other soluble constituents leak out. Triphenylmethane dyes were shown to block the internal utilization of glutamic acid in resting as well as growing cells, from which it is concluded that the interference is with a phase of the amino-acid metabolism not involved in growth and protein synthesis.¹⁰⁶ One such reaction blocked by triphenylmethane dyes is the formation of glutamine through phosphorylation of glutamic acid in the presence of adenosine triphosphate (ATP).⁹³ It was quite clear that neither penicillin nor sulfathiazole interfered with this utilization of glutamic acid, even under conditions of growth.

Sulfathiazole did not prevent glutamic acid assimilation by the cell wall. In growing cells only, it did block the internal utilization of glutamic acid. This blocked metabolism, however, was quite distinct from that described above, since it involved the condensation of glutamic acid residues into peptide or protein structures.¹⁷

Streptomycin

Streptomycin owes its unique position to its preferential selectivity for gram-negative and acid-fast organisms. It is unquestionably bactericidal for growing cells,¹⁰⁷⁻¹⁰⁹ and unlike that of penicillin, the killing rate increases as the concentration is raised.¹¹⁰ Strauss¹¹¹ asserts that the drug is bactericidal even for resting cells, but at a higher threshold, this suggests a different action mechanism from penicillin, which was only effective against growing cells, but conditions have not been made sufficiently comparable to settle this point unequivocally. The same investigator, and others,¹⁰⁹⁻¹¹² report morphologic abnormalities occurring at bacteriostatic levels.

To the pharmacologist it is of some interest that streptomycin is a glycoside (Fig. 3).¹¹³ Like other

demonstrated that the integrity of the cell-wall RNA of gram-positive forms is especially dependent upon reduced —SH groups⁹⁷⁻⁹⁸. Furthermore, staphylococci becoming resistant to penicillin and growing in its presence undergo two noteworthy changes: they adapt themselves to the higher oxidation-reduction potential by employing a wholly aerobic respiratory system¹⁰⁴, at the same time they become gram-negative, and acquire the ability to synthesize the amino-acids whose assimilation was formerly mediated by the cell-wall RNA^{93, 101-103}.

Evidence bearing upon the detailed mechanism of streptomycin action is still scanty. Sulfhydryl systems and RNA are both implicated by the few facts already established. Evidence that the drug can combine in a specific way with sulfhydryl compounds has already been reviewed. Streptomycin is reported to form a reversible complex with RNA, in competition with hydrogen ion and other cations¹¹⁵. The investigators suggest that although no enzyme is inhibited, RNA turnover is nevertheless disrupted, since access of enzyme to substrate is prevented. The preferential affinity of streptomycin for gram-negative forms is not clarified but may be connected with the lipopolysaccharide character of the cell wall in these species and the mycobacteria.

Obviously the facts at hand do not yet permit unification of all the clues into a single satisfactory theory. It is becoming increasingly evident, however, that antibacterial agents that have proved useful by virtue of a high chemotherapeutic ratio (in contrast to the antiseptic-disinfectant group) owe this property to a very specific interference with metabolic steps that are not shared to any important degree by host tissues. Comparative biochemistry has revealed how startlingly similar are many of the catabolic pathways and the mechanisms for elemental syntheses in all species from microorganism to man^{151, 152}. Clearly, unique modes of protein synthesis and reduplication must underlie morphologic specificity. It is not surprising, then, that drugs that are to distinguish bacterium from bacterium and parasite from host should prove to interfere in a specific fashion with the pathway of protein synthesis.

(To be continued)

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to be intrinsically unstable, unless nourished by a never-ceasing flow of energy and substrates for the synthesis of protein. Interruption of the dynamic state allows irreversible denaturation of a critical system, probably nucleoprotein in nature. The denaturation of protein, in general, follows a course such that the decay of any particular molecule is unpredictable, but the *probability* that each molecule will decay in a given period can be stated. The manifest result of such a denaturation process is the logarithmic death curve, the *logarithm* of the number of surviving organisms being proportional to time.

Whether "death" produced by an antibacterial agent is reversible or permanent may be determined, at least in part, by the firmness with which the drug is bound by vital cell constituents. The classic experiments of Gegenbauer¹³⁹ showed that the loss of viability induced by mercuric chloride in cultures of *Staphylococcus aureus* was reversible by simple washing for a certain time, after which the cells could still be revived by hydrosulfide. After a critical period neither method sufficed. Reversibility by either method depended upon *both* the drug concentration and the duration of contact.

Some compounds of the antiseptic-disinfectant group (detergents, tyrocidine and chlorine) kill through an obvious lytic action on the cell wall. Others kill more subtly, at a rate suggesting direct inactivation of a single nucleoprotein molecule per cell (Rahn¹⁴⁰). These show a progressive increase in killing rate as concentration is raised, comparable to that seen in the effect of irradiation upon the reproductive mechanism. The same compounds at lower concentration stop growth and reproduction, but viability is not appreciably lost if organisms are soon enough removed from the antiseptic agent. Effects of this type are often associated with inhibition of respiration, both in growing cells and in resting cells supplied with substrate for combustion.^{141, 142} In many compounds, therefore, antiseptic action seems to result from primary interference with energy-yielding catabolic reactions. All the effects of the antiseptic-disinfectant compounds are exerted upon nongrowing as well as growing cells.

The view that the chemotherapeutics under discussion — sulfonamides, penicillin and streptomycin — act upon the anabolic, protein-synthetic phases of metabolism is supported by two fundamental properties shared by these drugs: they exert their characteristic actions only (or most strikingly) upon growing cells, and they do not inhibit the respiration of resting organisms or the combustion of added substrates in the absence of growth. The loss of respiratory activity in growing cultures involves only the *extra* respiration associated with growth. In both respects these chemo-

therapeutics differ sharply from the antiseptic-disinfectant group.

Their intimate connection with growth and protein synthesis is further suggested by what is known of their mechanisms of action. The sulfonamides interfere with utilization of PABA in the synthesis of PGA, methionine, certain purine bases and perhaps other essential substances. Recent work with *Neurospora* mutants bears out the view that PABA may be a precursor of methionine.¹⁴³ Yet the evidence indicates that PGA is probably not an intermediate in the formation of these various compounds.³² It is possible that PABA is a common precursor in a series of parallel reactions leading to different substrates for protein synthesis. If the purine bases thus formed are incorporated into nucleoprotein one would expect species-specific nucleic acids to antagonize the sulfonamides non-competitively. This has not yet been investigated. Gale's finding that under conditions of growth sulfathiazole prevented the condensation of glutamic acid into peptide is exactly what one would expect if PGA or other glutamyl-PABA compounds were essential substrates in the process of protein synthesis.

Recent advances in nucleoprotein research have led to the conclusion that ribonucleic acid (RNA) occupies a central role in protein synthesis. It has been suggested that "nucleic acids serve as the agents which funnel energy into the protein synthesizing mechanism."¹⁴⁴ Rapid growth is associated with a high turnover of RNA.^{145, 146} It seems significant that penicillin, at bacteriostatic concentration, inhibits ribonuclease, mononucleotidase and phosphatase, which together are involved in the depolymerization and dephosphorylation of RNA.¹⁴⁷⁻¹⁵⁰ Furthermore, RNA is, to date, the only substrate, whose oxidation by nongrowing cells is inhibited by penicillin.⁷⁷

RNA is again involved in the specific uptake of glutamic acid by gram-positive organisms, this assimilation being inhibited by penicillin during growth. The unusual sensitivity of the gram-positive group to penicillin could be attributed to a high affinity of the drug for this cell-wall RNA system, the combination leading to a glutamic acid deficiency for growth. Gram-negative organisms, although less sensitive, are nevertheless acted upon by penicillin. It must therefore be assumed that the drug disrupts RNA turnover within both types of cell.

The observations of Pratt and Dufrenoy on the —SH to S—S shift induced by penicillin, and those of Cavallito and his co-workers on the specificity of combination of penicillin with sulfhydryl compounds, have not yet been integrated into the picture. Ribonuclease, if it is a sulfhydryl enzyme, or its substrate, RNA, may require reduced sulfhydryl groups, or may be otherwise sensitive to an increased oxidation-reduction potential. It has, in fact, been

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 35031

PRESENTATION OF CASE

A forty-seven-year-old unmarried woman was admitted to the hospital because of "inability to keep food down."

The patient stated that approximately one year before entry she had begun to have occasional vomiting after meals. This was attributed to nervousness. The vomiting became progressively more frequent, and eight months prior to admission it occurred once a day. She was always able to get liquid and soft foods down but could not swallow meat or other solids. When she attempted to eat solid food it "stuck" at the level of the lower end of the sternum, and in a few minutes the material was

regurgitated, unchanged in appearance. There was no nausea or hematemesis. When she was successful in swallowing a piece of solid food she experienced pain in the region of the lower sternum and even more severe pain in the back at the lower thoracic level. The pain was dull in character and lasted about two hours. Milk of magnesia sometimes eased the distress. During the following months, until the time of admission, she was forced to restrict the diet to egg-nogs, fruit juices and beef broth. She had lost 30 pounds in weight but had regained 8 pounds during the month before admission. There was considerable malaise. There was no melena, diarrhea or constipation. A roentgenogram in another hospital showed a stricture at the lower third of the esophagus, and she was subsequently referred to this hospital.

Four years before entry the patient cut her fingers on a glass. This was followed by intermittent attacks of coldness in the fingers, and the wounds became ulcerated and then gangrenous. A nerve block on the left side by injections for two weeks was carried out, but this did not help so a bilateral cervical sympathectomy was done. After a few weeks it was considered necessary to amputate the fingers and thumb of the left hand as well as the index finger of the right hand. Later the patient's feet began to remain cold all the time, and subsequent to this a bilateral lumbar sympathectomy was performed. She had no apparent progression of the disease since that time. She had been very

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and only minor dysphagia. The localized narrowing in these cases is about 4 or 5 cm above the diaphragm and constitutes an abrupt change. Esophagoscopy revealed smooth scar tissue consistent with some ulceration about the stricture. The lumen of the stricture in one case was extremely small, there was also diffuse esophagitis from the middle third of the esophagus down to the area of the constriction or to a point about 4 or 5 cm above the stomach. There was absence of normal peristalsis in the lower two thirds of the esophagus, accounting, they thought, for the impeding of swallowing fluid. The burning substernal pain they accounted for by the regurgitation of acid gastric contents through a relatively atonic cardia. They emphasized the fact that these constrictions occur at a point 5 cm above the diaphragmatic opening as a result of previous ulcerative esophagitis at that area, the latter developing because of interference with normal esophageal peristalsis as a result of sclerodermatous changes. This must, of course, be a rare cause of esophageal obstruction, but the association here with the changes that this woman had in her hands and feet makes it an interesting possibility for speculation.

Did this patient have scleroderma? It is hard for me to determine, — perhaps it would still be hard had I seen the patient, — but the impression I get is that in true Raynaud's disease the sclerodermatous changes appear late in the disease, if at all. The troubles that this woman had with ulcerative, gangrenous changes in the fingers certainly came on rather quickly. It is true that vascular manifestations may be the ones that bring the sclerodermatous patient to the physician. In one series of 40 cases about 25 per cent complained early of coldness and intermittent vasospasm,³ these phenomena becoming more and more prominent and occurring as in our patient with higher temperatures and possibly preceding skin changes by some time.

With these possibilities in mind let us ask Dr Wyman to show the films to see if the constriction bears any relation to these few cases of obstruction recorded with scleroderma.

DR F DENNETTE ADAMS Is it not usually a progressive disease? Would you not expect it to be?

DR BAKER I suppose it is, but there must be a few cases — and I shall ask Dr Lerman to comment later — in which it is largely restricted to the hands and feet, and less obviously to the face and chest, in which there is no pronounced progress.

DR EDWARD B BENEDICT I might say that the esophagus is involved in scleroderma in only a small percentage of cases. I have seen several cases, most of which showed severe esophagitis with some stricture and hemorrhage and erosion.

DR STANLEY M WYMAN The first two films are from an examination done elsewhere. They show the area of narrowing in the esophagus described in the protocol. There is a suggestion of an overhang-

ing margin on the right lateral border of the esophagus above the narrowing. We have insufficient filling of the stomach or duodenum on this film to comment on Dr Baker's question about the association of duodenal ulcer. I think it should have been looked for. There is, I believe, a definite, small, hiatus hernia. Examination done at the Eye and Ear Infirmary again shows the same diffuse narrowing with a suggestion of a small collection of barium on the right posterior aspect of the narrowed esophagus. The examination done here



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Physical examination revealed a thin, well developed woman in no distress. There was a Grade I blowing systolic murmur heard along the sternal border. The aortic second sound was greater than the pulmonic. The lungs and abdomen were normal. The fingers and thumb of the left hand and the index finger of the right hand were missing. The skin of the remaining fingers was thick.

The temperature, pulse and respirations were normal. The blood pressure was 120 systolic, 60 diastolic.

Examination of the blood disclosed a white-cell count of 10,200. The hemoglobin was 15.3 gm. The urine sediment contained 1 or 2 white cells per high-power field. The blood nonprotein nitrogen was 17.0 mg., and the total protein 5.6 gm. per 100 cc. The prothrombin time was 15 seconds (normal, 16 seconds).

An electrocardiogram showed slight left-axis deviation.

A roentgenogram disclosed an annular defect of the distal esophagus about 5 cm. above the diaphragmatic opening (Fig 1). The actual defect measured 1 cm. in length, with rather marked shelving above. Most of the compression appeared to be on the right and posterior side of the esophagus.

On the fourth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR MYLES P. BAKER. I think it might be instructive in discussing this case to put ourselves in the position of the ward officer confronted with this history and physical examination and discuss the diagnostic possibilities with just this verbal report of the x-ray examination in mind and then view the films later. Doubtless the nature of the deformity disclosed by x-ray study is going to be important diagnostically.

We are dealing with a middle-aged woman who developed dysphagia, regurgitation without nausea and substernal pain after swallowing solids for a year, coming on three years after symptoms, either of Raynaud's disease involving the hands and feet or scleroderma with Raynaud's phenomenon, the so-called acroscleroderma, had appeared. The diagnostic possibilities seem to me, first, that she had carcinoma of the esophagus, causing the filling defect in the lower third of the esophagus. It must be considered regardless of any other associated abnormalities found on physical examination. The symptoms that the woman complained of are in keeping with that diagnosis — namely, early minor dysphagia, substernal pain, reported as present in 75 per cent of cases of carcinoma of the esophagus

and frequently radiating to the back, and regurgitation of food, mentioned by Vinson¹ as not being particularly common with cancer, and by others as being present in some 20 to 65 per cent of cases. Weight loss, marked in this case, is characteristic of the disease. The weight loss in this case was not progressive. The absence of anemia or marked hypoproteinemia might be looked on as a favorable sign indicating that one was not dealing with carcinoma of the esophagus. There must be cases of carcinoma, however, that present no anemia in which the patients look surprisingly well nourished.

Another possibility is benign stricture of the esophagus. The position of the obstruction here is 5 cm. above the diaphragmatic opening and is probably compatible with benign stricture of the esophagus and certainly much more so than with the entity cardiospasm, which is due to obstruction in the interdiaphragmatic segment of the esophagus — lower down than we have any evidence of in this case.

What basis have we in the history for any cause of benign stricture of the esophagus? There is no mention of chemical trauma, no antecedent acute infection and, indeed, nothing of history compatible with recurrent peptic esophageal ulcer, nor have we an x-ray report of the presence of diaphragmatic hernia or short esophagus, which are recorded as being so frequently associated with demonstrable peptic ulcer of the esophagus. We have no comment about the presence of a duodenal deformity such as a man might have who had had an active duodenal ulcer in the past — a finding frequently observed in patients with peptic ulcer of the esophagus.

We do have, however, this unique and, in the protocol, emphasized association of esophageal stricture with a past history of serious disease affecting the hands and feet, the precise diagnosis of which is a little difficult to be certain about on the data presented here. It is well known that real disturbance in esophageal function may be an early symptom in scleroderma, a disease that is certainly a rarity to me and, with esophageal symptoms, a combination that I personally have never seen. I found a reference to this association of esophageal troubles and scleroderma in an article by Lindsay, Templeton and Rothman.² They report 5 cases with varying degrees of esophageal stenosis in 3. Their first patient had initial symptoms of dysphagia due to benign esophageal stricture for one and a half years before developments similar to Raynaud's disease made their appearance. The third patient developed substernal pain one hour after eating food, with some relief on taking alkalies — as our patient had — followed about six months later by numbness and coldness of the fingers, with benign stricture of the upper border of the phrenic ampulla, as did their second patient, with scleroderma of two and a half years' standing,

and only minor dysphagia. The localized narrowing in these cases is about 4 or 5 cm above the diaphragm and constitutes an abrupt change. Esophagoscopy revealed smooth scar tissue consistent with some ulceration about the stricture. The lumen of the stricture in one case was extremely small, there was also diffuse esophagitis from the middle third of the esophagus down to the area of the constriction or to a point about 4 or 5 cm above the stomach. There was absence of normal peristalsis in the lower two thirds of the esophagus, accounting, they thought, for the impeding of swallowing fluid. The burning substernal pain they accounted for by the regurgitation of acid gastric contents through a relatively atonic cardia. They emphasized the fact that these constrictions occur at a point 5 cm above the diaphragmatic opening as a result of previous ulcerative esophagitis at that area, the latter developing because of interference with normal esophageal peristalsis as a result of sclerodermatous changes. This must, of course, be a rare cause of esophageal obstruction, but the association here with the changes that this woman had in her hands and feet makes it an interesting possibility for speculation.

Did this patient have scleroderma? It is hard for me to determine, — perhaps it would still be hard had I seen the patient, — but the impression I get is that in true Raynaud's disease the sclerodermatous changes appear late in the disease, if at all. The troubles that this woman had with ulcerative, gangrenous changes in the fingers certainly came on rather quickly. It is true that vascular manifestations may be the ones that bring the sclerodermatous patient to the physician. In one series of 40 cases about 25 per cent complained early of coldness and intermittent vasospasm,³ these phenomena becoming more and more prominent and occurring as in our patient with higher temperatures and possibly preceding skin changes by some time.

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disease but also associated with various other conditions such as uremia

DR WYMAN Did this woman have a duodenal ulcer?

DR MALLORY None was found

DR BAKER This was more than esophageal ulcer and spasm — definite stricture?

DR MALLORY Definite ulceration with marked scarring and narrowing of the lumen

DR KING Is it your impression that most of them are lower than this?

DR MALLORY Yes, this was relatively high

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- 2 Lindsay J R, Templeton F E, and Rothman S Lesions of esophagus in generalized progressive scleroderma *J A M A* 123 745-750 1943
- 3 Allen E A, Barker N W, and Hill E A Jr *Peripheral Vascular Diseases* 571 pp Philadelphia Pa. W B Saunders Co 1946 P 232

CASE 35032

PRESENTATION OF CASE

A thirty-nine-year-old woman was admitted to the hospital because of easy fatigability, pain in the left anterior chest and the presence of an abdominal mass

One year before admission the patient first noted a sharp pain in the left anterior chest. The pain radiated across the left anterior chest to the axillary line, up into the axilla and down the inner aspect of the left arm to the wrist. At times the fingers became numb in association with this pain. About a year before admission she developed sharp, crampy, pelvic pain. There was no associated vomiting or bowel irregularity. The menstrual periods became irregular, and the amount of flow decreased. A hysterectomy for fibroids was done nine months before admission, with relief of the pelvic pain. No pelvic masses, except for the fibroids, were seen at operation. An appendectomy and right oophorectomy had been done nine years before admission.

Physical examination revealed a left-lower-quadrant mass. The cul-de-sac was empty, and the mass, approximately 6 cm in diameter, rode up out of the pelvis. The heart was not enlarged, and the apical rate was regular.

The blood pressure was 160 systolic, 95 diastolic. Examination of the urine and blood was within normal limits. A Graham test was negative. A barium enema was reported as showing no evidence of intrinsic involvement of the colon, but the colon was displaced by an extrinsic mass (Fig 1).

On the fifth hospital day a laparotomy was performed.

DIFFERENTIAL DIAGNOSIS

DR GORDON A DONALDSON I doubt very much whether the first perusal of this history has left any of you colder than it did me. On looking at it further, however, it is possible to summarize some of the salient points and find that approximately a third of the history can be accepted as a definite fact — namely, that the patient had a hysterectomy and that the right tube and ovary had been removed earlier. My only comment about this portion of the history is that we would like to know why the right ovary was removed nine years earlier. What was



FIGURE 1

the lesion? I am a little suspicious of a fibroid causing sharp, crampy, pelvic pain and wonder if something was overlooked in the pelvis nine months before at the time of laparotomy. Also, I would call attention to the cautious statement "no pelvic masses, except for the fibroids" were noted at this time. I wonder how much search was made for the left ovary.

So we are left with a thirty-nine-year-old woman with pain in the upper part of the torso and a mass in the lower part of the torso, both on the left side. It is always dangerous to make two diagnoses at these conferences, but unless the x-ray film can help us considerably I think we may be forced to

biopsy properly taken from the area of constriction. Both the history and the x-ray examination, as Dr Benedict has pointed out, are inconclusive in obstructive lesions of the esophagus, and only by direct observation and by study of biopsy material can one be sure of what one is dealing with and of a proper decision about procedure.

As far as the diagnosis is concerned, in this particular case I would favor that of benign stricture rather than that of carcinoma of the esophagus. Whether it has any relation to the associated peripheral vascular disease or true acroscleroderma is worthy of mention.

DR DONALD S KING Where does the so-called string sign come into a lesion like this, Dr Wyman?

DR WYMAN I think the lesion is too high for it.

DR JACOB LERMAN Patients with Raynaud's scleroderma syndrome certainly show many bizarre manifestations. The course is variable. Sometimes the sclerodermatous lesions dominate, and sometimes the Raynaud symptoms. In answer to Dr Adams's question we have seen patients who have progressed so far and then remain stationary for years.

Another point worth bringing out is that the sclerotic process that is present in the extremities is a universal process, and similar changes are seen in the myocardium and other organs. Some of these patients develop malnutrition as a result of the constant vomiting and with it an esophagitis on top of the esophageal fibrotic process, so that the picture on x-ray examination will be altered from time to time. The x-ray film shown is consistent with benign stricture complicated by esophagitis.

DR BENEDICT I do not know the diagnosis or treatment in this case, but I assume that the operation performed was esophagoscopy with biopsy, since that is the only sure way to differentiate benign stricture from carcinoma. The importance of taking a biopsy cannot be overemphasized because the treatment of benign stricture is bouginage, whereas the treatment of carcinoma is resection.

DR SOUTTER This woman was just as much a problem for us as she was for Dr Baker today. On the ward we did not believe she had clinical evidence of scleroderma. We discussed that diagnostic point and concluded that she did not have scleroderma of the esophagus. The report from the esophagoscopist and the roentgenologist was that carcinoma could not be ruled out. The esophagoscopist did not see anything more than the upper limit of the lesion. He was not able to obtain an adequate biopsy. We thought that we would have to explore this woman's esophagus because of the possibility of carcinoma. Furthermore, in many people who have benign strictures there is more dilatation of the esophagus above the stricture than there is in these films.

In the operating room we found the esophagus thickened over a small area at about 8 cm above

the cardia. It was a dense type of thickening, and we could not decide on palpation whether it was some benign lesion in the wall of the esophagus extending through the muscularis or whether it was a carcinoma. A few years ago in a patient who presented a problem of this nature we opened the esophagus with a longitudinal incision, thinking we were probably dealing with a benign lesion but found a malignant one. Although that tumor was resected, we had recurrence in the chest cavity, which we thought was due to spreading the disease by cutting into the tumor. Therefore, in this case we believed that opening the esophagus in the presence of carcinoma might lead to metastases. So we could see no alternative but to resect the lesion.

DR BENEDICT Dr Soutter seems to be arguing that the fact that this esophagus was not dilated is in favor of carcinoma. I do not agree. It is true that in long-standing achylasia (cardiospasm) the esophagus becomes dilated, but not in benign stricture.

CLINICAL DIAGNOSIS

Carcinoma of lower esophagus

DR BAKER'S DIAGNOSIS

Benign stricture of esophagus, unknown etiology

ANATOMICAL DIAGNOSIS

Peptic ulcer of esophagus, with stricture formation

PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY The resected specimen showed a benign ulceration of the esophagus that had the characteristic histology of peptic ulcer. As is customary in such cases we found several islands of gastric mucosa in the esophagus. The wall of the esophagus beneath the area of ulceration was scarred and thickened, but we thought that that could be entirely explained as a secondary reaction to the ulceration of the mucosa and did not indicate a preceding sclerosis of the sclerodermatous type.

Following operation the patient developed progressive difficulties, the anastomosis failed to heal, and empyema developed. She died about one week postoperatively. At autopsy the remainder of the esophagus was free from any sclerotic changes. Sections from one of the nongangrenous fingertips showed endarteritic changes, nonspecific in character, such as are frequently seen in Raynaud's disease. There was nothing on which we could make a histologic diagnosis of scleroderma.

The only other finding of some histologic interest was marked cystic dilatation of the pancreatic glands, a lesion that I saw with some frequency in the Army and have seen very rarely in civilian life. In this case I have no explanation for it. I have seen it in people very severely ill for a week or more before they die, frequently in cases of infectious

DR ADAMS Some time ago she was given an estrogen preparation for a while. It was stopped before hysterectomy. After that she received none. The note I made before she came to the hospital was that she had a mass up to the umbilicus.

DR MALLORY The question that I would have liked to ask at this point is whether the sponge count was certainly correct at the last operation.

DR ADAMS I did not ask that one.

DR WYLAND F. LEADBETTER Is the x-ray compatible with an anterior meningocele?

DR WYMAN There is no evidence of anything definite in the spine. It is a little unlikely to have anterior meningocele so low to the left of the midline, and it looks like two masses or a lobulated mass.

DR JOE V. MEIGS I have now seen three anterior meningoceles — two retroperitoneal at the midline, and the third on the left side. One could feel them fairly well.

DR MALLORY Are there any suggestions from the x-ray point of view?

DR WYMAN This is a homogeneous soft-tissue density that may be lobulated or may be multiple.

DR DONALDSON It is very unlikely for a lymphoma to present such a picture. I will stick to my diagnosis of endometrioma.

CLINICAL DIAGNOSIS

Ovarian cyst

DR DONALDSON'S DIAGNOSIS

Endometrioma

ANATOMICAL DIAGNOSIS

Hematoma of broad ligament and sigmoid mesentery

PATHOLOGICAL DISCUSSION

DR MALLORY Dr. Parsons, will you take up the story?

DR LANGDON PARSONS The chest pain is obviously a red herring, and I did not have to con-

sider that because Dr. Adams told me to let that alone. This mass was not in the pelvis, but rode up above it to the level of the umbilicus. Aside from the history the strongest point against ovarian cyst was that at pelvic examination the mass did not descend at any point into the pelvis. At operation we were confronted with a voluminous, blue-domed cyst lying between the broad ligament and the leaves of the sigmoid. At first I thought it was an ovarian cyst, but I soon found that I could not get around it and that it was retroperitoneal. It was actually pretty much on a level with the pole of the kidney, and the majority of it lay within the leaves of the sigmoid mesentery. I found a normal left ovary. As far as I can reconstruct this thing I believe that at the last operation the stump of the retained ovary was buried between the leaves of the broad ligament. Hemorrhage followed, and the hematoma gradually spread from the broad ligament into the sigmoid mesentery. We evacuated the hematoma, which drained about two liters of bloody fluid, and took a few biopsy specimens from the wall of the cavity.

DR MALLORY Our fragments from the wall showed only granulation tissue, organizing blood clot and hemosiderin, all evidences of old hemorrhage. We looked for endometriosis and found no evidence of it.

DR PARSONS We have talked about the rarity of cysts of the retained ovary. I do not think that we see many.

DR ADAMS Did you say that you found the left ovary?

DR PARSONS A normal left ovary.

DR MEIGS We do not see many cysts in retained ovaries — in fact, extraordinarily few. We have only seen one or two in the Vincent Memorial, although we leave an ovary in whenever possible in women who have not reached the menopause.

DR F DENNETTE ADAMS May I interrupt at this point to answer some of these questions When the appendix was taken out the ovary was said to have a cyst in it and was also removed Both operations were done in another city The story I obtained on the second operation was that the uterus was deformed, not by fibroid tumors, but by some congenital abnormality The left ovary was said to have been removed with the uterus Both operations were done by a capable surgeon in another city

DR DONALDSON Can we accept that as a fact?

DR ADAMS All I can say is that the surgeon who did the operation is highly capable and that the uterus and the left ovary were reported to me, although not by the surgeon, to have been taken out

DR DONALDSON May we see the x-ray films?

DR STANLEY M WYMAN The gall bladder is normal The plain film of the abdomen shows a soft-tissue fullness in the pelvis, slightly more to the left, and rising up into the abdomen, overlying the sacrum It appears larger on the film than it seems from the description of the physical examination One cannot be sure if this is a lobular mass or includes two or more separate masses The barium-enema examination shows the sigmoid to be displaced upward, apparently by a mass in the true pelvis, with a second mass or possibly a lobule of the mass rising above it at this point The bones appear normal as far as I can see on these films The masses are homogeneous and show no calcification

DR DONALDSON This is a huge mass that developed in nine months, and I still believe, from its position in the x-ray film, that it must have been related to the base of the broad ligament, perhaps the ovarian pedicle Was the hysterectomy total?

DR ADAMS I think it was I could not feel the cervix when I did a pelvic examination — for what that may be worth

DR DONALDSON We can eliminate the colon because of the lack of history and the negative barium enema Prolapse of an organ high in the abdomen such as the stomach or kidney or omental tumor is very unlikely I still believe that our information concerning the left ovary is not completely black and white, and we should still consider the possibility of disease in the left ovary or remnant of the left ovary As a matter of fact, I am really thrown off guard by the added information that the left ovary was absent I had a good story worked out for it One was a fibroma, the Meigs syndrome, an unlikely possibility, however, because of the site of the chest pain The tumor was described as 6 cm long, which is just about right for a fibroma This tumor is much larger than that, and the possibility of carcinoma with metastasis to the lungs came to mind, but the patient seemed to be in too good shape to have had a metas-

tatic lesion in the lung for a full year I suppose we ought to consider a residual, simple cyst of the left ovary

Finally, an endometrioma with pulmonary metastases is something that has been reported I glanced through the literature and found that there have been pulmonary metastases from endometriomas of the ovary This picture is consistent with that, but perhaps, again, the size of the tumor throws out that diagnosis An endometrioma 6 cm in diameter could have developed over the course of a year in a thirty-nine-year-old woman, and it is probable that she could have had symptoms from a properly placed metastasis in the left lung

DR ADAMS May I interrupt again because I believe that the history is not fair to Dr Donaldson This pain in the chest had existed, to my knowledge, for two and a half years The patient described what sounded like anginal pain, but I do not believe she actually had angina The pain in the chest existed long before any of the pelvic symptoms appeared

DR DONALDSON I wondered if it was cardiac pain She was slightly hypertensive, perhaps menopausal

DR ADAMS That was the only observation of high blood pressure I always found her pressure normal in my office

DR DONALDSON Because of the lack of any history of angina and the presence of numbness in the fingers it is an unlikely possibility

The possibility of a cervical rib or tight anterior scalene muscle as a cause of such pain might be considered It is unusual for such a syndrome to produce pain in the anterior chest wall itself We ought to consider perhaps a slowly growing lesion of the chest wall or of the lung, such as a Pancoast tumor with metastases to the pelvic organs Again, the patient was too young and apparently too well, and the history too long I think it would be unusual for this woman to have such a lesion I believed that endometrioma with metastases to the lung was the best bet Against this is the fact that the tumor was so large, but I suspect that an endometrioma could have developed to this size in nine months' time

DR JOHN McL MORRIS Is there a chest film?

DR ADAMS It was normal How recently it was done, I do not know

DR TRACY B MALLORY Are there any other suggestions?

DR GRANTLEY W TAYLOR A mass 6 cm in diameter riding out of the pelvis would not push the transverse colon up I wonder if Dr Adams has a note on that

DR ADAMS I felt it, so it must have been pretty big

A PHYSICIAN Was she given estrogen for the menopause?

to do their share, and promptly, in implementing the program that is being planned

There is today one vital consideration for physicians to remember. They must work in harmony if they are to achieve through their own initiative those things that others believe can be achieved better by methods of compulsion

HEMODYNAMICS IN THE LUNGS

UNTIL comparatively recently, knowledge of abnormal changes in the blood pressure in the pulmonary circuit has been largely speculative. It is now possible to make direct measurements of the blood pressure in the arterial portion of the pulmonary circuit and to relate abnormalities in such pressures to clinical and post-mortem findings. The full implications of such studies, now being carried out in a number of laboratories, are likely to be profound.

Pulmonary hypertension has been recognized as a rather indefinite clinical entity for many years. Pulmonary vascular sclerosis has been familiar to pathologists since the middle of the last century. One of the most illuminating, if somewhat neglected, monographs on the latter topic is that by Ljungdahl,¹ which appeared in 1915. In this work, sclerotic changes in the pulmonary vessels were shown to be relatively frequent in mitral stenosis and to occur in certain congenital cardiac lesions, notably patent ductus arteriosus, in some cases of pulmonary emphysema and in the obscure and rare entity known as primary pulmonary vascular sclerosis. It is also likely that such vascular disease occurs in some cases of cardiac decompensation on a hypertensive or arteriosclerotic basis.

With the modern technics now available it is possible to study in the living patient the alterations in pulmonary arterial blood pressure that have, largely by implication, been said to accompany pulmonary vascular sclerosis. Of much greater importance is the likelihood that, by establishing the presence of pulmonary arterial hypertension, the investigator can predict the presence of vascular changes within the lung. Such information not only may prove to be of great prognostic value but also may be of considerable value to the surgeon when the proposed operations for mitral stenosis become a practical matter.² The

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FISH OR CUT BAIT

THE medical profession, which has made such impressive advances along clinical and scientific lines, must decide, and shortly, whether it has also the ability and the interest to maintain and control and modernize its own time-honored standards of service.

To do this it must sacrifice certain of its cherished beliefs of other days. It must to some extent submerge, for the sake of a wider distribution of its benefits, that personal independence and freedom of action so characteristic of the private practitioner of medicine. It must freely acknowledge that any form of voluntary health insurance that offers a decent standard of medical care to all economic and social groups is more effective than the individually bestowed charity for which it has been so conspicuous, and that has always been so freely given

It must realize that it is functioning in a world in social revolution, and that slow evolutionary processes of change are not adequate to bring it up to the times and keep it abreast of them. It must understand that the only apparent alternative to such a remodeling of its methods is capture and eventual domination by other forces that, lofty as their motives may be, have yet but a limited understanding of the traditions, the ideals and the technics that they seek to control.

The profession of medicine must, and must now, come fully awake to its responsibilities, to the dangers that threaten it — and to its own strength. It must make up in a few brief months for years lost in the cultivation of its public relations. It must teach a forgetful public what that public owes it, it must acknowledge openly what it owes the public, and present its plan of payment. It must acknowledge its inertia, its blunders and its former indifference to public opinion, and wash them out.

It must show its receptiveness to new ideas and its ability to discuss their common problems with all agencies that are honestly seeking the same goal of service.

To do these things now and effectively requires money — not a war chest or a slush fund, as it has been termed by the chief protagonist of compulsory insurance, who has the resources of a federal agency with which to promulgate his own ideas — but an educational fund to put clearly before the public the accomplishments and the capacities and the honest intentions of a free but united profession.

The proposed assessment is necessary in order that the American Medical Association, *representing the medical profession of the country*, may put its relations with the public on a sound basis. If the assessment is paid with some scolding and a lecture, then let it in that way be given, for criticism may serve two purposes — to relieve the critic and, so far as it is constructive, to guide the recipient. The important thing is for every member of the profession now to rally to the support of his ancient and honorable calling, to show his pride in it and to contribute to the maintenance of its standards and its prestige. The secretary of the Massachusetts Medical Society, acting in this instance only as an agent of the American Medical Association, is taking the steps necessary to collect the assessment for the parent organization. The physicians of Massachusetts are urged

to do their share, and promptly, in implementing the program that is being planned

There is today one vital consideration for physicians to remember. They must work in harmony if they are to achieve through their own initiative those things that others believe can be achieved better by methods of compulsion

HEMODYNAMICS IN THE LUNGS

UNTIL comparatively recently, knowledge of abnormal changes in the blood pressure in the pulmonary circuit has been largely speculative. It is now possible to make direct measurements of the blood pressure in the arterial portion of the pulmonary circuit and to relate abnormalities in such pressures to clinical and post-mortem findings. The full implications of such studies, now being carried out in a number of laboratories, are likely to be profound.

Pulmonary hypertension has been recognized as a rather indefinite clinical entity for many years. Pulmonary vascular sclerosis has been familiar to pathologists since the middle of the last century. One of the most illuminating, if somewhat neglected, monographs on the latter topic is that by Ljungdahl,¹ which appeared in 1915. In this work, sclerotic changes in the pulmonary vessels were shown to be relatively frequent in mitral stenosis and to occur in certain congenital cardiac lesions, notably patent ductus arteriosus, in some cases of pulmonary emphysema and in the obscure and rare entity known as primary pulmonary vascular sclerosis. It is also likely that such vascular disease occurs in some cases of cardiac decompensation on a hypertensive or arteriosclerotic basis.

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surgeon may logically expect to obtain his best results in patients who have not developed pulmonary vascular sclerosis and therefore to urge operation relatively soon after the valvular lesion is discovered. Similarly, in cases of patent ductus arteriosus, complete relief from symptoms after ligation should probably not be predicted if the pulmonary arterial pressures and clinical symptoms indicate that advanced pulmonary vascular sclerosis is present.

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A few extracts from this report, which points out the deplorable conditions that exist for the care and treatment of mentally ill patients in the Commonwealth, are pertinent.

One of the greatest problems in the field of mental health, according to Dr Perkins, is the absence of any broadly based, mature application of an in-

formed public opinion to serve a state department as an intelligent, critical and effective supporter as the situation may from time to time demand. This statement of Dr Perkins is particularly applicable to the members of the medical profession, probably few of whom are well informed about the conditions as they exist.

In general, the report continues, the Department is responsible for providing for the efficient, economical and humane management of the state hospitals and may establish by-laws and regulations for the government of those hospitals, of which there are sixteen, caring for approximately 30,000 patients. It is pertinent also to realize that 95 out of every 100 persons in the Commonwealth who need mental hospitalization must be cared for in the state hospitals because they cannot afford the price of private facilities. For better or worse, the State has a practical monopoly—the fate of the mentally sick citizen is literally in its hands.

The report furthermore shows clearly that the responsibilities mentioned are not being adequately met. The Commissioner points out that World War II materially reduced over-all medical standards in the state program because of the inability of the Commonwealth to compete in the manpower crisis, and the inexorable demands of the armed forces. Recovery has not yet been made from that reduction of standards.

Basically, there are “not enough well trained doctors or nurses or occupational therapists or other personnel indispensable to the proper bedside care of patients and execution of therapeutic programs either within the hospital or the clinics.”

The quotas allowed for the work by the state are less than the standards deemed minimum by nation-wide agencies in the field of mental health, but even these quotas are not met. In the quota allowed for physicians there was as of September, 1948, a vacancy of 25 1/4 per cent, in the ward services the vacancies amounted to 30 8/8 per cent.

The loss of every trained doctor, according to the report, entails years of training for the physician who is to replace him.

Mere swapping of holders of M.D. degrees does not make up for the loss. The doctors we have lost almost without exception have gone where they can get more cash, have less restrictions in regulating their lives, where more adequate personnel is available in the ancillary fields to help them in their work.

Doctors, like other scientific men, will take just so much pushing around financially and otherwise. Compared with the competition, the Commonwealth has failed to realize this fully.

The Commissioner in this statement puts his finger on the fact that to provide a satisfactory medical service the pay must be on a competitive basis, but there must be, in addition, a proper atmosphere in which a physician can flourish. He further points out that teaching and training activities constitute one of the best ways of maintaining an active and alert staff and emphasizes the importance of research as an outlet for an active staff.

Unless the conditions for the care and treatment of the *mentally ill* patients are promptly improved, there can only occur a demoralization that is bad for both the community and the medical men who make up a part of the community. It appears that the physicians of the Commonwealth, individually and through their medical societies,—state, district and local,—would be well advised to inform themselves of the conditions as they exist and take an active part in their improvement.

HISTORY OF PHARMACY

THE first Pan-American Congress of Pharmacy, meeting in Havana late in 1948, gave official recognition to the American Institute of the History of Pharmacy at the University of Wisconsin. The Institute was named “as the center of the endeavor in the history of pharmacy in America.”

Through a more formal representation of Latin American countries in the Institute, with a trustee in each of them, it is hoped that investigations into the history of pharmacy will be broadened and a series of monographs may be published on the history of pharmacy in all the countries of this hemisphere. Among the more practical aspects of the congress was the discussion concerning unification of official drug standards and the publication of a Pan-American pharmacopeia.

Practicing, during the development and progress of his ancient profession, similar forms of magic and mystery, the pharmacist finally emerged as a true scientist at about the same time as did his co-partner in the investigation of drugs, the physician. Modern medicine owes much to this continuing partnership.

CORRESPONDENCE

REGARDING THE AIA ASSESSMENT

To the Editor You may have seen the recent press statement that those who control policy in the American Medical Association have voted to assess all members \$25 each. And that the proceeds (\$3,500,000) are to be "spent on a campaign of 'education' to tell people the advantages of the 'American system' of medical care." There is no evidence that this sum will be used in an unbiased search for facts or in the promotion of impartial discussion. On the contrary, judging by past editorials in the *Journal of the American Medical Association*, the actual purpose is to influence opinion in one direction by presenting one side of a controversial issue.

This is not education, it is propaganda. Should American doctors be subjected to such an extraordinary tax without their consent? Even if such action by the American Medical Association officials should be pronounced legal I believe that it is unethical.

Therefore, I suggest that the *New England Journal of Medicine* and the Massachusetts Medical Society openly oppose any such tax until a referendum has been held.

It would be possible for a voting slip to be inserted in each copy of the *Journal of the American Medical Association* for one issue after January 1. Until some such referendum is held I have no intention of paying this tax.

HENRY S. FORBES, M.D.

Milton, Massachusetts

To the Editor The many inquiries concerning the recent decision of the House of Delegates of the American Medical Association to assess each member \$25.00 indicate a need for clarification of many aspects of this charge. Very little information is provided by the editorial in the *Journal of the American Medical Association*, which announces the decision and states that the purpose is "to provide a fund adequate for meeting the proposal of the present administration and particularly the present Federal Security Administrator to nationalize the services of the medical profession through the enactment of a compulsory sickness insurance act covering every person in the United States."

Before paying the assessment many doctors want to know (indeed should know, if they are to act as intelligent physicians and citizens) a few simple things about the assessment: Is the money raised to be spent by the county medical societies, by the state medical societies or by the American Medical Association? Is it to be spent merely in opposing by reiterating, as Mr. Baruch says, "what not to do" or by proposing constructive action? If the constructive action pertains to voluntary insurance will endorsement of voluntary plans be limited to Blue Cross Hospitalization and Blue Shield Medical Service or will well organized plans such as The Health Insurance Plan of New York City, the Permanente Foundation Health Services of California and the Labor Health Institute of St. Louis be encouraged? Will opposition to General Hawley's proposals concerning Blue Cross and Blue Shield continue?

Many doctors, particularly the younger members who may have little vested interest in current medical practice and but little professional or other income want to know if this assessment is compulsory in the sense of losing membership or good standing in the county and state medical societies and hence the American Medical Association, or even of receiving prejudiced consideration as applicants to or members of hospital staffs.

That young physicians can fear such a possibility is not only a serious reflection upon the ethics of the profession but also a serious threat to the future of the American Medical Association. Up to now membership in a county and state medical society and the American Medical Association has frequently been used as a qualifying requirement for positions on many hospital staffs or other professional privileges. If membership becomes contingent upon paying an assessment that more than doubles the income of the American Medical Association and is to be used to oppose legislation endorsed by the President of the United States and the majority party of Congress a major purpose of the American Medical Association becomes not only political but also highly controversial. Under such circumstances if political rather than professional considerations determine membership, can the American Medical Association continue some

of its important roles? For example, can membership any longer carry a connotation of professional qualification that places nonmembers at a disadvantage?

Compared to jeopardizing such traditional functions the question of what will happen to the American Medical Association's tax status as an educational and nonpolitical organization is of minor concern. In this connection one wonders why the House of Delegates decided to have the American Medical Association raise this money itself rather than continue having it done by the National Physicians Committee, which already ranks as one of the top lobbying organizations in the country.

Many of these questions must have been debated by the House of Delegates in arriving at its decision to make the assessment. That the debate was held in executive session, therefore, seems unfortunate for it is unlikely that members of the House would have said things that the public should not hear, and its answers to many questions should be enlightening. If the debate provides them, it would appear deserving of publication. If not provision for tolerant discussion and considered debate seems essential to a democratic professional behavior to an enlightened professional opinion and to a respect for that opinion by the public.

Ironically should discussion be suppressed and physicians pay the assessment under compulsion, would not the American Medical Association be practicing what it professes to abhor—namely, domination by a federal or national body of state and county units that constitutionally are autonomous?

I trust that the Massachusetts Medical Society will deal with this matter according to its traditionally New England democratic way.

ALLAN M. BUTLER, M.D.

Massachusetts General Hospital
Boston

To the Editor The people's mandate, handed down at the polls on November 2, 1948, is frequently interpreted as requiring federal participation in the provision of less expensive and more extensive medical care for the American people. Whatever physicians may have believed before November 2 the attitude of the public toward health legislation should be reasonably plain at present. Whether the entry of the federal Government into the field of medical care on a large scale is wise or foolish, the possibility of it is nearer than ever before. Blind opposition to this possibility is an invitation to disaster. Neither the medical profession nor any other professional or occupational group can successfully defy the majority rule in the United States as now constituted. For the profession to attempt such defiance would be tragic indeed, it would inevitably mean the lowering of organized medicine in the eyes of the public to the position of an economic pressure group, surely an ignominious decline from a position deserving and receiving the faith and trust of layman and physician alike.

The Government's plans to solve the nation's medical economic problems have been published for all to see. Mr. Oscar Ewing the federal security administrator, and his advisers have produced a plan that they believe will meet our needs. The plan includes provision for compulsory health insurance a feature that may well be neither desirable nor necessary at the present time. Be that as it may no reasonable person can doubt that Mr. Ewing and his colleagues have made a serious effort to master an enormously complex socioeconomic problem and to provide effective remedies acceptable to the nation as a whole. It is ridiculous to regard the plan as the instrument of Leninism, and it is naïve to believe that, even if made into law without a change, it would communize American medical practice. It is just as ridiculous to accept it as the perfect answer to the nation's needs or to assume that it must pass the Congress unchanged and unamended. Meek acquiescence on the part of the profession to the bill as it now stands is unthinkable.

If the profession must accept the near-reality of federal participation in the provision of medical care what, then, should be its attitude toward the Ewing Plan? A specific, point-by-point answer is urgent and for it to be effective it must concern itself primarily with improved standards of medical care and secondarily, if at all with the status of the physician. The tremendous uproar over medical care in this country and the objections of the medical profession to plans and planners have centered too much on the prestige, the

dignity and the rights of the physician. Improvement of medical standards as a primary goal has been sadly obscured by both groups. The Ewing Plan is an economic plan designed to provide abundant, low-priced medical care to everyone, but not concerning itself specifically with improving the standards of medical practice. Similarly, the profession's objections to the plan have been based largely on the protection of free enterprise and the status quo, either by direct statement or by implication, although medical standards have occasionally been dragged in to underscore an economic point. The unfortunate tendency of some professional groups to concern themselves primarily with financial matters led one highly respected medical spokesman, H. J. Morgan, in an article entitled "Professio" (*Ann Int Med* 32:887-891, 1948) to say:

One of our so-called professional organizations has emphasized economics and the material aspects of medical practice so vociferously and forcefully as to lead some of the people and some of the people's representatives in government to consider it a business or trade organization. A Federal Court decision revealed in no uncertain terms that Medicine in the United States, in this instance, forfeited its professional status before the law. It appears that by word and deed we interpreted ourselves to the people and the courts as tradesmen.

It is still not too late to do our own house cleaning. An effective plan embodying federal participation, must be evolved by the profession itself, and it must be one that will inspire the confidence instead of the distrust of the public. The plans offered by organized medicine to date have been defensive plans, designed to change the *status quo* as little as possible. An entirely new approach is essential. It must be based primarily on the intent to distribute high-grade medical care as widely as possible. There must be no reluctance to alter the *status quo* merely because of fear of change. The profession must set up its considered plan for the ideal system of medical care. No stop-gap compromise will suffice as a master plan. From its plan for the ideal system, the profession and other medical planners can then proceed to arrange the details, economic and otherwise, to suit the circumstances. An imaginative and courageous approach of this sort will stand in sharp contrast to the grumbling and lusterless schemes currently being brought forward by the profession to counter the popular, but usually defective, offerings of Government planners.

The perfect solution has not yet been presented. It is the medical profession itself that must evolve and present it. There should be no more jousting at windmills. The profession should brutally scrutinize its own conscience, examine the facts and set the pace, not only for the political planners but also for itself. By audacious and sober action, it can regain its position as the profession of integrity and unassailable standards. If its actions continue to be motivated merely by blind resistance to change it will reap catastrophe, the full extent of which no man can now foresee.

CARLETON B. CHAPMAN, M.D.

Minneapolis, Minnesota

To the Editor: Certain recent inquiries and comments concerning the action of the American Medical Association in assessing its members twenty-five dollars are disturbing. Hypercritical comments from those committed to compulsory national health insurance have validity commensurate with their underlying logic. Adverse criticism based on lack of information is entirely another matter.

At the annual meeting of the American Medical Association in Chicago in June the House of Delegates voted to raise the levying level through dues or assessment to twenty-five dollars. The extensive activities of the parent organization have been heretofore conducted without dues or assessment other than the amount paid for subscription to the *Journal of the American Medical Association*. At the recent interim session conducted in St. Louis the full House of Delegates for reasons sufficient to our delegates unanimously voted the maximum assessment.

There may well be valid criticism of the existing structure of our medical house. Minority opinion may not be adequately represented. But certain basic facts are valid. The House of Delegates of the American Medical Association

is composed of state-society members elected on a proportional basis. When we castigate the American Medical Association in public we are castigating ourselves. When the house is on fire is no time for a jurisdictional dispute over who should man the hose.

The St. Louis assessment because of its urgency could not apparently be discussed in advance of the meeting. The response to the assessment as voted has not been good in the press generally and has been universally poor among the more vocal proponents of federal planning.

Most of us need information on the basic facts at issue. An extensive educational campaign for physicians and for the public is immediately forthcoming. A few million dollars for the job to be done is inconsequential in view of its importance.

Final judgment on the assessment should be withheld until the reasons that produced a unanimous vote of the House of Delegates are made known to all of us. This information is on the way. In the meantime, one aspect of this issue is clear. Our delegates have acted. Our organization has acted. Are we with it?

JOHN F. CONLYN, M.D.

Boston

BOOK RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Diagnosis in Gynaecology. A classification of gynaecological diseases based on aetiology and the clinical logic for diagnosis. By James V. Ricci, M.D., clinical professor of gynecology and obstetrics, New York Medical College, director of gynecology of the City Hospital, New York, director of gynecology and obstetrics, Columbus Hospital, attending gynecologist and obstetrician, Flower and Fifth Avenue Hospitals, New York, and consultant in gynecology and obstetrics, Beekmantown Hospital, New York. 8°, cloth, 259 pp. Philadelphia: The Blakiston Company, 1948. \$4.50.

This manual is based on the clinical demonstrations given to students of the New York Medical College. A fundamental knowledge of gynecology is necessary for its profitable use. A new type of classification by genital structures and their diseases is used instead of the usual classification by diseases. The preliminary chapters are devoted to the general subjects of anatomy, female sex hormones, diagnosis and symptomatology and general classification. A good index concludes the volume. The book is well published.

NOTICES

ANNOUNCEMENT

Dr. Joseph A. Dubins announces the removal of his office to 314 Commonwealth Avenue, Physicians Hall, Boston.

NORFOLK DISTRICT MEDICAL SOCIETY

A meeting of the Norfolk District Medical Society will be held at the Boston Medical Library, 8 Fenway, Boston, on Tuesday, January 25, at 8 p.m. The following scientific program, entitled "Geriatrics," will be presented:

Problems of the Aging Theodore G. Klumpp, M.D.

The Surgical Care of the Aged John Homans, M.D.

Medical Aspects of Growing Old Robert T. Monroe, M.D.

The meeting, which will be followed by a collation, is open to all physicians.

NORFOLK DISTRICT WOMEN'S AUXILIARY

A meeting of the Women's Auxiliary of the Norfolk District Medical Society will be held in the State Suite, Copley Plaza Hotel, Boston, on Tuesday, January 25, at 3 p.m. Miss Elizabeth Wilson, actuary, statistician and author, will speak on the subject "Socialized Medicine in England."

(Notices concluded on page xiii)

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INVOLVEMENT OF THE ILEUM IN CHRONIC ULCERATIVE COLITIS*

FRED J. MCCREADY, M.D.,† J. ARNOLD BARGEN, M.D.,‡ MALCOLM B. DOCKERTY, M.D.,§ AND
JOHN M. WAUGH, M.D.¶

ROCHESTER, MINNESOTA

THE fact that extension of the inflammatory process to the terminal portion of the ileum occurs in patients with chronic ulcerative colitis is fairly well known, but it has not received sufficient emphasis. The ileocecal valve does not limit the progress of the lesions of ulcerative colitis into the terminal part of the ileum any more than it prevents secondary involvement of the colon from the ileum in cases of regional enteritis. The type of chronic ulcerative colitis that begins in the rectum and spreads orad may in many cases extend into the terminal part of the ileum, it may continue for great distances up the ileum, and in a few cases it may involve even the jejunum.

It is a well recognized and established fact that so-called regional or segmental or right-sided colitis is associated with a high incidence of ileal involvement. Crohn, Garlock and Yarnis¹ reported the incidence of involvement of the ileum in these cases to be as high as 8 per cent. Borgen and Weber² likewise cited a high incidence of ileal involvement in these cases — namely, 63 per cent. It must be kept in mind that this type of colitis comprises only a very small percentage of all cases of chronic ulcerative colitis. In this paper we are not concerned with the segmental type of colitis, furthermore, we have excluded from this study specific types of inflammation of the ileocecal coil such as those caused by tuberculosis, amebiasis and actinomycosis. We have therefore included only cases of diffuse chronic ulcerative colitis of the thrombo-ulcerative variety — the streptococcal type described by Borgen and Weber² — that characteristically begin in the rectal segment and spread cephalad and, in time, involve the whole colon. It is this variety that makes up the vast majority

of the cases of ulcerative colitis encountered clinically.

To restrict this study to ileums that had been diseased secondary to the type of chronic ulcerative colitis defined above, only cases in which the lesions showed the typical and characteristic proctoscopic and roentgenologic features of this form of colitis were selected. In all the cases the first signs of inflammation were related to the rectum and distal segments of the large bowel as determined on the basis of proctoscopic findings. The shortening and deformity of the entire colon consistent with this type of colitis was noted roentgenologically in all the cases in which studies were made with the aid of barium enemas. These cases were analyzed to determine the incidence, extent, pathological nature, clinical significance and prognosis of ileal involvement in cases of chronic ulcerative colitis.

MATERIAL AND METHODS

This paper comprises a complete pathological study of 23 post-mortem specimens of bowel in cases of diffuse chronic ulcerative colitis in which the ileum was involved and of 6 surgical specimens that included a small segment of the involved terminal part of the ileum, which had been resected along with part or all of the diseased colon. The cases were encountered at the Mayo Clinic from 1935 through 1946.

The clinical records were carefully reviewed to ensure that the cases studied fell into the category already referred to. For this, reliance was placed on the proctoscopic and roentgenologic data. All cases not conforming to these criteria were purposely omitted.

All the gross specimens, surgical and post mortem, utilized in this study had been preserved in 10 per cent formalin at the Mayo Clinic Museum. Each gross specimen was inspected to determine the nature and extent of the gross involvement of the ileum. Multiple blocks of tissue were removed from various areas of ileal involvement. These blocks were placed in a fresh 10 per cent solu-

*Abridgment of a thesis submitted by Dr. McCready to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

†Fellow in surgery Mayo Foundation University of Minnesota Medical School.

‡Professor of medicine Mayo Foundation University of Minnesota Medical School.

§Associate professor of pathology Mayo Foundation University of Minnesota Medical School.

¶Associate professor of surgery Mayo Foundation University of Minnesota Medical School.

tion of formalin, sectioned on a freezing microtome, stained with hematoxylin and eosin and mounted permanently on glass slides. The slides were studied carefully for the type and extent of ulceration and inflammatory invasion in each of the coats of the ileum.

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McKittrick and Miller,¹² in 1935, placed the incidence of ileal involvement in chronic ulcerative colitis at 1.3 per cent in their cases. In 1941 Cave¹³ reported that in 8 out of 81 cases (10 per cent) of chronic ulcerative colitis there was involvement of the ileum. McMillan,¹⁴ writing in 1942, declared that nearly 25 per cent of the cases of diffuse ulcerative colitis were associated with "backwash" into the terminal portion of the ileum. He also commented on the rarity of hyperplastic and granulomatous types of inflammatory reactions in the ileum. In 1944, in describing his technic for ileostomy, Cattell¹⁵ observed that he had found involvement of the ileum in approximately a sixth of his operative cases; he cautioned against making a stoma in an ileum that was involved in an inflammatory process. In the same year Crandon, Kinner and Walker¹⁶ reviewed reports of 16,500 consecutive autopsies to determine the frequency of ileal involvement. They found 44 cases in which chronic ulcerative colitis was considered the cause of death. In 17 of these cases, or 39 per cent, there was simultaneous involvement of the small intestine. Dennis,¹⁷ in 1945, probably found the highest incidence (33 per cent) of ileal involvement in this disease from his observations at the time of operation. Before proceeding to do an ileostomy, he routinely resected a small segment of intestine for immediate gross pathological study to rule out ulcerative ileitis at this level. He found the presence of diseased bowel at the site of ileostomy to predispose to the development of postoperative diarrhea and a fecal fistula. Thus, the incidence of ileal involvement reported in the literature varied from 1.3 to 39 per cent.

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Most authors, including Baird,¹⁸ Barger,¹⁹ Cave,¹³ Colp,²¹ Crohn and Rosenak²² and McMillan,¹⁴ who have observed ileal involvement in chronic ulcerative colitis apparently believed that it merely represented a retrograde extension of the inflammatory process through the ileocecal valve, a sort of "backwash" into the terminal portion of the ileum. Crohn and Rosenak,²² in describing the gross pathological appearance of the ileum in chronic

ulcerative colitis, contended that the disease in the ileum is a destructive and denuding process as it is in the colon. They differentiated the process grossly from that seen in primary ileitis in that the ileum failed to present the hyperplastic, stenotic and granulomatous appearance that is characteristic of primary ileitis but showed only the flat superficial ulcerations characteristic of the colon in chronic ulcerative colitis. To show how chronic ulcerative colitis can involve the ileum they described a striking example in which the ulcerations caused by colitis involved the ileum in a previously made ileosigmoidal stoma, with subsequent perforations of the ileum and generalized peritonitis. Mallory²³ described a case, encountered at autopsy, of chronic ulcerative colitis with ileal involvement and brought up the question of the pathologist's ability to differentiate on anatomic and histologic grounds, the ileum in chronic ulcerative colitis from the ileum in regional ileitis. He expressed the belief that these two different clinical entities can be definitely distinguished from each other on the basis of the pathological appearance of the ileum.

Mallory²⁴ described the histologic picture of regional ileitis, referring to the characteristic and typical pseudotubercle formation, the marked inflammatory invasion of the deeper layers of the bowel wall and the tendency to fistula formation, in contrast, he commented on the absence of these features in the ileum involved as a result of extension of chronic ulcerative colitis. Ulceration and denudation seemed to these authors to be the prominent gross pathological features in the ileum involved as a result of extension of chronic ulcerative colitis.

Although Cave²⁰ recognized the probability that ileal involvement in chronic ulcerative colitis occurs as a result of a continuation or spread of the process backward through the ileocecal valve, he mentioned the fact that in 7 of the 80 patients on whom he operated primarily for ulcerative colitis, he found inflammatory lesions in the small intestine resembling those of regional enteritis.

Few writers have discussed the complications of ileal involvement in chronic ulcerative colitis. Castleman²⁵ reported a case of chronic ulcerative colitis in which perforation of the ileum occurred. The ileum was remarkably hemorrhagic and thin, and when it was opened there were numerous ulcers measuring 1 to 2 cm in diameter, 3 of which had perforated. These ulcerations had appeared proximal to a previously made ileal stoma. Crandon, Kinney and Walker¹⁶ reported 2 cases of ileal perforations proximal to ileal stomas in chronic ulcerative colitis, the lesions in these ileums were identical with those found in the colon in chronic ulcerative colitis. They presented supportive evidence that the process had existed, at the time of operation, in the ileum above the site elected for enterostomy. These authors also reported a remarkably high

incidence of perforation of the small bowel in their cases. Perforation occurred in lesions of the ileum in 4 of the 17 cases in which there was involvement, an incidence of 24 per cent. This was even higher than the incidence of perforation in the colon itself, which was 16 per cent.

Jankelson, McClure and Sweetsir,²⁶ in 1945, reported 11 cases of acute perforation of the bowel in chronic ulcerative colitis, the mortality rate from the complication being 100 per cent. In 4 of these 11 cases, or 36 per cent, the perforation was in the lower part of the ileum. In the remaining 7 cases some segment of the colon was involved. Corbett,²⁷ writing at the same time, in discussing the complications of ileostomy stated that abscesses and fistulas into adjacent structures and the abdominal wall often formed proximal to the stoma as a result of perforating lesions in the diseased ileum in chronic ulcerative colitis. He reported 2 cases, in 1 of which death occurred as a result of this complication.

MAYO CLINIC SERIES

Incidence of Ileal Involvement

In the selection of the 29 cases that are the subject of this study, the data on 103 cases of diffuse thromboulcerative colitis were reviewed. All these cases satisfied the proctoscopic and roentgenologic criteria for this study, as outlined above. The data in 81 of these 103 cases were based on post-mortem observation, in 23 of the 81 cases, or 28 per cent, there was definite evidence of ileal involvement. The data in 22 of the 103 cases were based on surgical findings, 6 of the surgically resected colons in these 22 cases showed involvement of the attached ileal segment, an incidence of 27 per cent. The incidence of ileal involvement in the 103 cases of chronic ulcerative colitis was 28 per cent.

Incidence by Age and Sex

Of the 29 patients, 15, or 52 per cent, were males. Twenty-four, or 83 per cent, of the patients were in the first three decades of life, and 5, or 17 per cent, were in the fourth decade. The youngest subject was thirteen years old, and the oldest was forty-seven.

Nature of Disease in Ileum

Gross findings An analysis of the pathological features of the 29 specimens that formed the basis for this study showed that the ileum was affected by one of two inflammatory processes. In 22 cases the terminal portion of the ileum presented a gross pathological picture similar to that found in the corresponding colon—that is, the ileal segment was completely and diffusely involved in ulcerative changes (Fig 1, 2 and 3). In the other 7 cases separate ulcers appeared intermittently in the ileum, the intervening portions of small intestine remaining essentially normal (Fig 4). In all 29 cases the in-

tion of formalin, sectioned on a freezing microtome, stained with hematoxylin and eosin and mounted permanently on glass slides. The slides were studied carefully for the type and extent of ulceration and inflammatory invasion in each of the coats of the ileum.

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None of the 29 specimens showed either diffuse or localized thickening of the wall of the ileum, even though in a few cases the corresponding wall of the colon was excessively thickened, with marked stricture of the intestinal lumen. Although it was quite obvious even to the naked eye that there was



FIGURE 5 Section of the Entire Wall of the Ileum in a Case of Diffuse Thrombo-ulcerative Colitis

Note the mucosal ulcerations. The submucosa, muscularis and serosa are essentially normal. The wall is not thickened (hematoxylin and eosin stain — $\times 8\frac{1}{2}$)

no great thickening of the involved ileal walls, a measurement of the thickness was made in all cases, it was found that in none was the wall more than 3 or 4 mm thick. In 26 cases the thickness was within the normal limits of 2 or 3 mm. None of the walls resembled the thick boggy ileal walls seen in specimens representative of regional enteritis. As we expected in the absence of thickening of the ileal walls, none of the 29 ileums revealed any stenosis of the intestinal lumen such as that frequently seen in regional enteritis.

Extent of involvement. The ulcerations may involve only the last few centimeters of the ileum, or they may be scattered over a distance of a few feet. Occasionally, they are found simultaneously in the upper part of the ileum and jejunum. It was possible to determine the exact extent of ileal involvement only in the post-mortem specimens (23 in number) because in only these cases was all of the small bowel available for examination. In the 17 cases in which there was diffuse involvement of the terminal part of the ileum, the average length of ileum affected was 20 cm, the shortest being 4 cm and the longest 45 cm.

Of the 7 specimens presenting patchy intermittent ulcerations, 3 showed ulcers that extended intermittently over several feet of the lower and upper portions of the ileum, and the other 4 revealed simultaneous involvement of both the ileum and the jejunum with multiple, well defined ulcers. It is of some interest that of the 23 post-mortem specimens, at least 30 cm of the terminal part of the ileum was involved in 6 and 45 cm in 3.

In the 6 surgical specimens in which part of the ileum was resected along with the right portion of the colon, only a small segment was available for study, the longest being 50 cm and the average 20 cm. In only 3 of these surgical specimens was there enough obviously normal ileum proximal to the diseased segment to permit determination of the exact length of the part involved, in these cases 12 cm of the ileum, on the average, was affected. In the other 3 the inflammatory change was present over the whole segment of the terminal portion of the ileum and ran right up to the point of resection. The length of the ileal segment involved was 4, 5 and 30 cm, respectively, but for reasons stated above, if more of the ileum had been available, perhaps the length of diseased ileum would have been even greater.

Microscopical findings. As was seen from a review of the gross specimens, ulceration and denudation were the predominant features in the mucosal coat (Fig. 5). Ulceration of some degree was present in the ileum of all 29 specimens, in some it was superficial and consisted mostly of erosions and atrophy of the epithelium, but in others it was deep, with a good deal of sloughing and necrosis. An attempt was made to place the ulcers of the ileum, on the basis of microscopical appearance, in the following three groups according to their depth of penetration: ulceration to and including the muscularis mucosae (20 specimens), ulceration through the submucosa (4 specimens), and ulceration through the main muscular layers and serosa with perforation (5 specimens). It was noted that the depth of the ulcers was independent of their gross distribution and character. Many of the solitary ulcers penetrated through all the coats of the bowel, whereas many of the diffuse ulcerations were superficial in character and were associated with little inflammatory invasion of the other coats.

Histologically, in the base of the ulcers the usual three typical zones were seen: zone of necrosis, zone of inflammatory reaction characterized by edema, vascular engorgement and infiltration with polymorphonuclear leukocytes, lymphocytes and plasma cells, and zone characterized by the presence of various amounts of granulation tissue and collagenous connective tissue.

Some authors classify ulcers as acute or chronic. Twenty-four of the specimens showed ulcerations that were chronic, with a predominance of lymphocytes and plasma cells and only a mild degree of

flammatory reaction was much milder and far less advanced than that seen in the diseased colon. This is in agreement with previous observations made by Rankin, Bagen and Buie.¹¹

The severer degree of inflammatory changes in the ileum was found in the 22 cases in which the

lines of longitudinally running ulcerations. The ulcers were irregular and exhibited a great deal of undermining and coalescing. The gross features

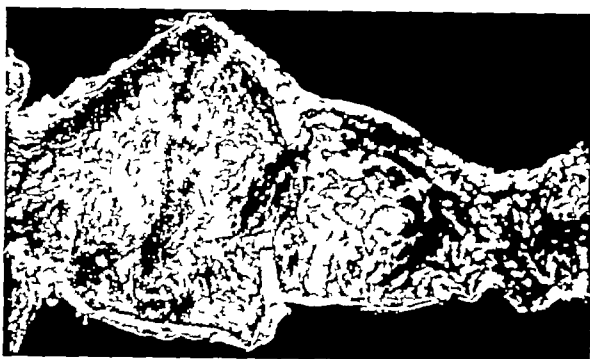


FIGURE 1 *Diffuse Thromboulcerative Colitis Affecting the Cecum, with Extension through the Ileocecal Valve to Involve the Terminal Portion of the Ileum*

Note the diffusely ulcerated and denuded mucosal surface of the ileum and the absence of any appreciable thickening of the wall

terminal part of the ileum presented to the naked eye the same gross appearance as that found in the chronically diseased colon. The ulceration of the mucosa of the ileum in these cases was so marked



FIGURE 3 *Diffuse Thromboulcerative Colitis of the Entire Colon, with Extension into the Terminal Portion of the Ileum*

in these cases resembled greatly those of polyposis cystica of Virchow, which also is characteristically manifest in the colon in the same cases.

In the other 7 cases the disease was not quite so denuding or destructive, although ulcerative changes in the ileum occurred. These specimens did not reveal the involvement as a diffuse process continuing back from the colon but showed multiple ulcers that had a scattered or patchy distribution, leaving variable amounts of relatively nor-



FIGURE 2 *Diffuse Thromboulcerative Colitis in the Colon, with Some Extension into the Terminal Part of the Ileum. The terminal segment is diffusely ulcerated*

that there was almost complete loss of the mucosa except for a few polypoid islands of mucosa. There was complete loss of the transverse folds and villi of the ileum. The inflammatory process represented a direct continuation of the changes in the colon through the ileocecal valve, characterized by long

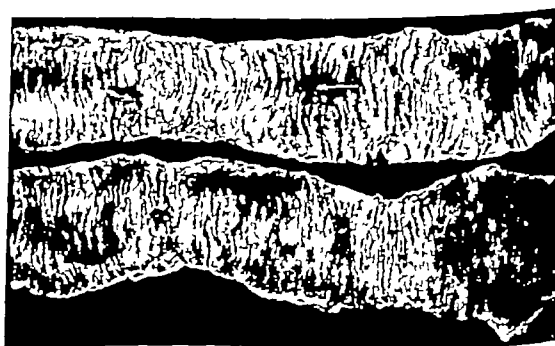


FIGURE 4 *Segments of the Ileum in a Case of Chronic Ulcerative Colitis, Showing Solitary Scattered Ulcers of the Ileum*

mal mucosa between them. These ulcers, which varied from 2 cm to 2 or 3 mm in diameter, were for the most part irregular in shape, although round

or oval ones were occasionally seen. The long axes of the solitary lesions were either longitudinal or transverse in relation to the ileum. The bases of the ulcers were for the most part fibrotic and granular in appearance. The edges were sharp and well defined. Occasionally, the surrounding mucosa was reddened or congested, but more often the near-by tissues were completely free of evidence of any gross inflammatory reaction. The ulcerations did not have any constant relation to the mesentery as seen in regional enteritis but were distributed over the whole lumen of the small intestine.

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Some authors classify ulcers as acute or chronic. Twenty-four of the specimens showed ulcerations that were chronic, with a predominance of lymphocytes and plasma cells and only a mild degree of

acute polymorphonuclear leukocytic reaction. The 5 specimens that revealed marked degrees of acute inflammatory change were those in which ileal ulcers had resulted in perforation.

In 15 of the 29 cases there was a mild to moderate proliferative thickening of the muscular elements of the muscularis mucosae but not to the marked degree that is seen in cases of regional enteritis. Throughout the submucosa there was a minimal degree of edema, chronic nonspecific granulation tissue and cellular infiltration with aggregations of lymphocytes, mononuclear cells and plasma cells.



FIGURE 6 Diffuse Thrombolytic Colitis of the Entire Colon, with Involvement of More than 30 cm of the Terminal Part of the Ileum

Only the 5 specimens with more acute ulcerations displayed any great degree of polymorphonuclear leukocytic infiltration, and this was found at the base of the ulcers. There was moderate dilatation of the lymphatic channels and congestion of the blood capillaries. Hemorrhage and thrombosis, features described by Bargen¹⁹ as characteristically appearing in the colon, were present in most of the sections but not to the same pronounced degree as seen in the colon. The most characteristic feature was the comparatively minor edematous fibroblastic reaction and fibroplasia, which was minimal when compared with that which is found in the submucosa in cases of regional enteritis.

There was no obvious hypertrophy of the internal and external coats of the muscularis propria in any of the 29 cases. Except in the 5 cases in which there was penetration of the ulcer to the serosal layer and general peritonitis along with the usual degree of thickening with inflammatory exudate, the serosa

was normal in all respects in the 29 cases. Small focal collections of epithelioid cells, lymphocytes and giant cells without caseation, referred to as pseudotubercles, were not seen in any of 29 cases of chronic ulcerative colitis, whereas in 30 per cent of the cases of regional enteritis this is a fairly frequent finding. Hadfield,²⁸ Owens²⁹ and Shapiro³⁰ have made reference to this finding in regional enteritis. A study of lymph nodes and mesentery was by necessity omitted from this investigation inasmuch as they were not available for the majority of specimens studied.

Roentgenologic findings. Of the 29 cases, in 10 there were no studies made with the aid of barium enemas, owing to the critical condition of the patient. In 4 of the remaining 19 cases the roentgenologic report mentioned involvement of the terminal part of the ileum by the pathologic



FIGURE 7 Diffuse Thrombolytic Colitis of the Entire Colon, with Extension into the Ileum for a Distance of Approximately 60 cm

process. A recent survey of the roentgenograms revealed definite evidence of ileal disease in another 6 cases, thus making a total of 10 cases of 19 (more than 50 per cent) in which ileal involvement was demonstrated by means of barium-enema studies. The average length of the segment involved as noted in the roentgenologic studies was approximately 1 foot (30 cm) of the terminal part of the ileum proximal to the ileocecal junction. This involve-

ment was continuous with that of the diseased colon. Eight of the 10 specimens showed at least 30 cm of involvement, and 2 showed involvement for only a few centimeters according to the roentgenograms. Frequently, the colon in chronic ulcerative colitis is so badly diseased that the roentgenologist does not report the ileal involvement even though roentgenologic evidence is present. Again, the competency or incompetency of the ileocecal valve during the time that barium-enema studies are being made probably plays an important part in determining roentgenologically the point to which the disease has extended into the terminal part of the ileum. Thus, a fair estimate of the true incidence of involvement cannot be obtained on the basis of roentgenologic studies alone (Fig 6 and 7).

Complications Clinical symptoms of mechanical obstruction of the small bowel due to stenosis of the lumen were not observed in any of the 29 cases of chronic ulcerative colitis in which the ileum was involved by ulcerative disease. This was to be expected on the basis of the study of the gross specimens, inasmuch as not a single specimen presented stenosis of the lumen of the small bowel or excessive thickening of the wall, which was found routinely in the cases of chronic regional enteritis.

It was impossible to estimate how often the ulcerations of the involved ileum gave rise to severe hemorrhage or loss of fluid because the process in the colon alone was enough to account for these occurrences. However, excessive loss of fluid from the ileum following an ileostomy has been shown by Crandon, Kinney and Walker¹⁶ to arise from these ulcerations. None of the 8 patients in this series who underwent ileostomy continued to bleed from the ileal stoma or to lose an excessive amount of fluid after operation, but it must be remembered that all these patients succumbed very shortly after operation. Only 1 of the 8 patients survived longer than three weeks, and he died within two months of the date of ileostomy.

Perforation of the ileal ulcers is without doubt the most dangerous of all the complications of ileal involvement in chronic ulcerative colitis because it apparently invariably results in generalized peritonitis and death. As mentioned above, in 5 of the 29 cases (17 per cent) this complication occurred. One patient presented six solitary ulcers, one of which had perforated after ileostomy. This patient died three weeks later of generalized peritonitis and multiple ulcers were demonstrated in the ileum proximal to the ileal stoma. Crandon, Kinney and Walker¹⁶ reported a 24 per cent incidence of perforative lesions of the small bowel in cases of ulcerative ileitis.

Clinical significance In attempting to evaluate the clinical significance of involvement of the ileum in chronic ulcerative colitis it should be demonstrated whether this involvement occurs relatively

early in the course of the disease or whether it is, for the most part, a very late complication — a sort of terminal event in the downhill progress of the disease. Therefore, it is important to know when the ulcers make their appearance in the ileum. Crandon, Kinney and Walker¹⁶ have shown that ileal involvement may appear early in the course of the disease. In an analysis of our 29 cases the only way that we could determine whether the ileum was involved relatively early or whether the involvement occurred merely as a terminal event in the course of the disease was by means of a study of the cases in which there was roentgenologic evidence of ileal involvement or by means of a study of the surgical cases. In 3 cases disease of the ileum was demonstrated roentgenologically one month, two months and three years respectively before death. In the 6 surgical cases, from one to seven years elapsed from the time that involvement was described at operation to the time of the present study. Certainly, in none of these cases could the involvement be called a terminal event of an intractable colitis, therefore, its occurrence must have been of more than academic interest.

A further analysis was made to determine whether the severity or course of colonic disease had any relation to the involvement of the ileum. We were interested in seeing whether the patients who had acute fulminating ulcerative colitis that might terminate fatally in a very short time were more prone to have ileal involvement than those with disease that was characterized by a long, chronic course of remissions and exacerbations. In 8 of the 23 cases in which autopsy was performed there had been a rather acute fulminating course of a year or less from the onset of symptoms to death, in the other 15 cases the course was chronic. Therefore, it is apparent that ileal involvement occurs both in cases of acute fulminating disease and in those of long-standing chronic disease. It is also of clinical significance that in only 1 of the 8 cases of acute disease were the ulcerations so severe that they resulted in perforation of the ileum. In the other 4 cases of perforation the disease was definitely chronic.

What, then, is the importance of ileal involvement in chronic ulcerative colitis? How may the prognosis be affected by this involvement? When an operation such as ileostomy is performed in this disease and the terminal part of the ileum is simultaneously involved in the inflammatory process, a high mortality and a poor operative result may be obtained.

Ileostomy in chronic ulcerative colitis is accompanied by a very high mortality. In 1932 Barga, Brown and Rankin²¹ reported a mortality of 66 per cent for emergency and 50 per cent for elective ileostomy. In 1935 McKittrick and Miller²² observed a mortality of 35 per cent. Cave and Thompson,²³ in 1941, reported an over-all mortality

acute polymorphonuclear leukocytic reaction. The 5 specimens that revealed marked degrees of acute inflammatory change were those in which ileal ulcers had resulted in perforation.

In 15 of the 29 cases there was a mild to moderate proliferative thickening of the muscular elements of the muscularis mucosae but not to the marked degree that is seen in cases of regional enteritis. Throughout the submucosa there was a minimal degree of edema, chronic nonspecific granulation tissue and cellular infiltration with aggregations of lymphocytes, mononuclear cells and plasma cells.



FIGURE 6 *Diffuse Thromboulcerative Colitis of the Entire Colon, with Involvement of More than 30 cm of the Terminal Part of the Ileum*

Only the 5 specimens with more acute ulcerations displayed any great degree of polymorphonuclear leukocytic infiltration, and this was found at the base of the ulcers. There was moderate dilatation of the lymphatic channels and congestion of the blood capillaries. Hemorrhage and thrombosis, features described by Bargen¹⁹ as characteristically appearing in the colon, were present in most of the sections but not to the same pronounced degree as seen in the colon. The most characteristic feature was the comparatively minor edematous fibroblastic reaction and fibroplasia, which was minimal when compared with that which is found in the submucosa in cases of regional enteritis.

There was no obvious hypertrophy of the internal and external coats of the muscularis propria in any of the 29 cases. Except in the 5 cases in which there was penetration of the ulcer to the serosal layer and general peritonitis along with the usual degree of thickening with inflammatory exudate, the serosa

was normal in all respects in the 29 cases. Small focal collections of epithelioid cells, lymphocytes and giant cells without caseation, referred to as pseudotubercles, were not seen in any of 29 cases of chronic ulcerative colitis, whereas in 30 per cent of the cases of regional enteritis this is a fairly frequent finding. Hadfield,²⁸ Owens²⁹ and Shapiro³⁰ have made reference to this finding in regional enteritis. A study of lymph nodes and mesentery was by necessity omitted from this investigation inasmuch as they were not available for the majority of specimens studied.

Roentgenologic findings. Of the 29 cases, in 10 there were no studies made with the aid of barium enemas, owing to the critical condition of the patient. In 4 of the remaining 19 cases the roentgenologic report mentioned involvement of the terminal part of the ileum by the pathologic



FIGURE 7 *Diffuse Thromboulcerative Colitis of the Entire Colon, with Extension into the Ileum for a Distance of Approximately 60 cm*

process. A recent survey of the roentgenograms revealed definite evidence of ileal disease in another 6 cases, thus making a total of 10 cases of 19 (more than 50 per cent) in which ileal involvement was demonstrated by means of barium-enema studies. The average length of the segment involved as noted in the roentgenologic studies was approximately 1 foot (30 cm) of the terminal part of the ileum proximal to the ileocecal junction. This involve-

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CANCER OF THE LOWER LARGE BOWEL*

Results in 100 Cases

ISAAC M WEBBER, M D †

PORTLAND MAINE

THE intent of this survey is to present an investigation of facts pertinent to the care of 100 consecutive patients with cancer involving the lower segments of the large bowel and to offer an appraisal of the therapeutic effort employed in their management.

This series includes both service and private patients at the Maine General Hospital, private patients at the Eye and Ear Infirmary and the Mercy Hospital, all of Portland, and one or more patients treated in each of six other institutions in outlying towns. It is obvious, then, that no one of these patients received all the advantages available in the university or large medical center. Furthermore, some of the results obtained reflect earlier and less experienced endeavor before the advent of the sulfonamide or antibiotic remedies and before the value of fluid, electrolytic, vitamin and protein deficiencies was fully appreciated.

From the current literature and from my own observation, the impression is gained that cancer of the large bowel is neither diagnosed nor subjected to operation appreciably earlier than it was ten or more years ago. Yet intestinal cancer, like any malignant lesion, has an early stage when the growth is small, sharply circumscribed and therefore readily extirpated. Just how long cancer in its early phase exists in the bowel without producing symptoms is yet to be determined, unfortunately, the process remains quiescent without manifestation until certain complications signal the presence of danger.

*Presented at the annual meeting of the New England Surgical Society, New Haven, Connecticut, October 1, 1945.

†Chief surgical staff, Maine General Hospital.

It is common knowledge that when a tumor of the bowel becomes sufficiently ulcerated the process may manifest itself by either gross or occult blood in the stool—an occult blood loss at times so insidious that only anemia is evident, the malignant lesion being otherwise asymptomatic. A cancerous mass, having acquired sufficient size and inflammatory reaction, or having compromised the bowel lumen, may produce enough irritation to promote frequent or liquid stools and in some cases dejections composed largely of mucus, either with or without local or abdominal discomfort as an associated symptom. These manifestations are the obvious signs and symptoms that warn both patient and physician of impending danger, but too many practitioners appear to be unmindful of the fact that such complaints indicate not early cancer but the complications of a well established malignant tumor urgently in need of attention.

Inasmuch as complaints referable to the terminal segments of the large intestine ordinarily bespeak the existence of a benign disorder, the average person with such an ailment is apt to assume that he is suffering from one of the more prevalent conditions such as piles, colitis and diarrhea and often employs self-medication for months. That the physician too often acquiesces in this frequently fallacious assumption or initiates the idea himself, instead of insisting that the patient have the benefit of a thorough rectal examination is perhaps only natural since it has been estimated that the average practitioner rarely encounters yearly more than one or two patients with cancer of the rectum and, therefore, is not rendered sufficiently cancer-

of 25 per cent for ileostomy, the rate being 50 per cent for emergency operations and 9 per cent for elective operations. In the same year Lahey³³ reported a mortality of 20 per cent for ileostomy in chronic ulcerative colitis. Many circumstances have been held responsible for the high mortality rate and the high incidence of failure of ileostomy in this disease. We wish to emphasize the fact that involvement of the ileum by ulcerative disease is one of the commonest and yet infrequently mentioned factors in the high mortality rate and the frequent failure of ileostomy in chronic ulcerative colitis.

Of course, it is agreed by most surgeons that extensive exploration of the peritoneal cavity and excessive handling of the diseased bowel in the acute stage of chronic ulcerative colitis is contraindicated. Nevertheless, enough exploration and examination of the distal part of the ileum must be done to exclude the diagnosis of inflammatory changes in this segment. Dennis¹⁷ has emphasized this point. He routinely sections a small segment of ileum for gross examination of the mucosa prior to establishing the site for the ileal stoma to avoid placing the stoma in a diseased segment of the small bowel. Involvement of the ileum in chronic ulcerative colitis is probably a definite contraindication to the performance of ileostomy unless the ileal stoma can be placed well above any area in which there is gross or microscopical involvement. Eight of the 23 patients who came to autopsy had had a previous ileostomy. The longest period of survival was sixty days, and the shortest five days.

SUMMARY AND CONCLUSIONS

A study is presented of 23 necropsy specimens of the bowel in cases of chronic ulcerative colitis of the diffuse thromboulcerative variety with ileal involvement encountered at the Mayo Clinic from 1935 to 1946. In addition, the ileum in 6 surgically removed specimens of the bowel in cases of chronic ulcerative colitis with ileal involvement was studied. These 29 specimens were selected from 81 autopsy and 22 surgical specimens of the bowel in cases of chronic ulcerative colitis in which the proctoscopic and roentgenologic criteria outlined were met. The incidence of ileal involvement in the 103 cases was 28 per cent. Six of the 22 surgically removed specimens showed ileal involvement, giving an incidence of 27 per cent, 23 of 81 autopsy specimens revealed such involvement, giving an incidence of 28 per cent. The incidence of ileal involvement reported in the literature varied from 13 to 39 per cent.

The average length of the segment of ileum affected in the cases in which the pathologic changes were diffuse was 20 cm., with variations from 4 to 45 cm. In 7 of the 29 cases solitary ulcers were present, sometimes extending throughout the length of the small bowel.

The nature of the disease in the ileum was similar to that found in the colon. It was essentially denuding and ulcerative. Twenty-two cases were diffusely ulcerative, and in 7 the ileum presented multiple solitary ulcers.

Roentgenologic evidence of ileal involvement was found in 10 of 19 cases in which barium-enema studies were carried out.

Perforation of the ulcerations of the ileum, with generalized peritonitis, was a very serious complication that occurred in 5 of the 29 cases, or 17 per cent. In 4 of the 5 cases perforation occurred almost immediately after the performance of ileostomy.

The duration of the disease showed no definite relation to the incidence of ileal involvement. Eight of the 23 patients who came to autopsy (35 per cent) ran an acute fulminating course of one year's duration or less, whereas the remaining 15 patients (65 per cent) had a long chronic course lasting from five to fifteen years.

Ileal involvement in chronic ulcerative colitis is not necessarily a terminal event of an intractable colitis as is assumed by many authors. In 9 of the 29 cases (31 per cent), the ileum was definitely shown, on the basis of surgical or roentgenologic data, to be involved relatively early in the course of the disease.

The ileum is involved in chronic ulcerative colitis more often than is generally realized, and this finding should therefore be looked for in all cases of diffuse chronic ulcerative colitis.

Knowledge of the presence and extent of ileal involvement in chronic ulcerative colitis is an important consideration if surgical treatment is deemed necessary.

Ileostomy for chronic ulcerative colitis performed through a segment of ileum that is the site of ulcerative inflammatory changes will probably produce a poor operative result. Perhaps this is one of the important considerations responsible for the high mortality associated with ileostomy in the treatment of this disease.

Involvement of the ileum is probably one of the factors that retard the healing process in the colon in chronic ulcerative colitis.

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Results in 100 Cases

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PORTLAND, MAINE

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Inasmuch as complaints referable to the terminal segments of the large intestine ordinarily bespeak the existence of a benign disorder, the average person with such an ailment is apt to assume that he is suffering from one of the more prevalent conditions such as piles, colitis and diarrhea and often employs self-medication for months. That the physician too often acquiesces in this frequently fallacious assumption or initiates the idea himself, instead of insisting that the patient have the benefit of a thorough rectal examination, is perhaps only natural since it has been estimated that the average practitioner rarely encounters yearly more than one or two patients with cancer of the rectum and, therefore, is not rendered sufficiently cancer-

conscious to recognize the fact that a malignant tumor should be the primary consideration to be confirmed or rejected only after appropriate investigation. Physicians do not appear constantly alert to the fact that 70 per cent of all cancer of the large intestine can be either actually palpated or made accessible to the eye by use of the sigmoidoscope, whereas it frequently escapes detection by the conventional barium-enema x-ray study.

Although progress in the field of establishing the presence of cancer in the earlier phases of its development is grievously lacking, ground has unquestionably been gained in the field of therapy. In recent years a greater number of the more extensive and inaccessible malignant tumors of the alimentary tract have been resected with increasing degrees of success. The fact has become well established that morbidity and mortality rates in the management of colonic and rectal cancers have definitely lowered, and, since the healing process of the body is influenced by a variety of factors, few surgeons have been sufficiently speculative to ascribe this more recent decline to any solitary factor.

In 1942, however, in reporting his experience with one-stage abdominoperineal resections, Jones¹ noted that the incidence of abdominal-wound infection was in direct relation to the number of

ment but to the activity of the sulfonamide compound. Furthermore, because of that same agent, the two most lethal complications of large-bowel resection fell precipitously, peritonitis from 6.1 per cent before the sulfonamide era to 1.8 per cent after it and, correspondingly, bronchopneumonia from 2.2 to 0.7 per cent.

Although the years 1940 and 1942, as mentioned respectively by Pemberton² and Jones,¹ may have witnessed a substantial decline in morbidity and mortality owing to the influence of single, solitary factors such as the innocuousness of suture material on the one hand and the bactericidal effect of sulfonamides on the other, it is noteworthy that the year 1942 has been designated by McKittrick³ as

TABLE 2 Hospital Deaths

GROUP	FATAL COMPLICATIONS	NO. OF DEATHS
First 50 patients (40 resections)	Bronchopneumonia	2
	Peritonitis	1
	Volvulus small bowel	1
	Cerebral hemorrhage	1
	Undetermined (no autopsy)	3
Second 50 patients (45 resections)	0	0

TABLE 1 Operative Procedures in 100 Cases of Rectal and Rectosigmoidal Cancer, 1933-1946

NO. OF CASES	PROCEDURE	DEATHS
14	Colostomy	6
1	Fulguration	0
9	Loop colostomy with anterior resection	0
5	Anterior resection and colostomy	2
22	Lahey two-stage resection	3
14	Anterior resection with end-to-end anastomosis	0
2	Cecostomy with abdominoperineal resection	0
33	Abdominoperineal one-stage resection	1
85	Resection	8 (9.4 per cent)

peritoneal and pulmonary complications. He expressed the opinion that postoperative peritonitis was always secondary to an infected wound, and he implied that, by removal of the hazard of infection from the incision by the use of steel wire sutures, peritoneal infection had been practically eliminated. Furthermore, during this period of the metallic suture, which was the only change in management, the incidence of hospital deaths dropped from 12 to 4.5 per cent, and he stated, "I am convinced that this type of closure is accountable for most of the success." During the year 1940 the morbidity and mortality in colonic and rectal surgery at the Mayo Clinic, according to Pemberton² also dropped rather abruptly from approximately 15 to 5 per cent. This improvement was credited not to a change in technic or manage-

the period of transition from the earlier to present methods. He has expressed the opinion that as the result of adherence to meticulous technic and essential basic surgical principles, without dependence on chemotherapeutic and antibiotic agents or on staged operations, the death rate of 11 per cent prior to 1942 has fallen to 3.6 per cent. In the present survey it is an interesting coincidence that of the first 50 patients, the 40 who underwent resection prior to the year 1941 suffered a 20 per cent hospital mortality but that of the second 50 patients the 45 who were subjected to similar treatment experienced no mortality.

An appraisal by the surgeon of his own work should be of assistance in modifying methods or practices for the benefit of those patients entrusted to his care. A prerequisite, of course, is that he know what is being accomplished by other workers in the same field of endeavor under similar as well as more favorable conditions and that he be familiar with the natural history of the disease under consideration. The latter information on rectal cancer in this country was made available in 1935 when Daland, Welch and Nathanson⁴ reported the end results in 100 untreated cancers of the rectum. In their record we find that, although a single patient lingered for forty-nine months, the median length of life was only fourteen months from onset of symptoms to death. All patients were miserable while they awaited the inevitable, and all died with cancer. Also during that period from 19 different hospitals, 10 of which were in Boston, these investigators found the prevailing operative mortality

to be 26 per cent and, operative deaths excluded, the five-year survival rate to be 41 per cent. Since these findings were recorded, mortality and longevity figures have continuously improved.

The various types of operative procedure employed in the group of patients here presented are recorded in Table 1. The wisdom exercised in performing 14 segmental resections with end-to-end anastomosis for cancer of the rectosigmoidal region can be properly questioned since such an operation does not remove the greatest possible amount of contiguous and regional lymph-node tissues. But regardless of the fact that Glover and Waugh⁵ justify the less radical operation with preservation of the anal sphincter as a result of their investigation of lymph-node metastasis in cancer of the "recto-sigmoid region," and despite the fact that Gilchrist and David⁶ present evidence against the advisability of such a procedure as a result of an investigation of the same problem, under certain conditions it has seemed to me that the interests of the patient could be best served by the less radical operation. Complete loss of vision, loss of vision with profound deafness, liver metastasis and an error in interpreting by palpation two hepatomas as metastatic growths were factors that influenced

TABLE 3 Contact Tissues or Organs Resected en Bloc with Primary Cancer

STRUCTURE	NO OF CASES	SURVIVAL
Uterus adnexa	1	2 da
Uterus	1	4 yr
Posterior vaginal wall and labium	2	3 yr* 4 yr*
Posterior vaginal wall	2	0† 2 mo
Bladder peritoneum and adventitia	1	11 yr
Ileum	1	9 yr
Appendix	1	3 yr

*Patient living

†Patient died on operating table

me to preserve the anal sphincter. A better service to others in this sub-group might have been derived from the more radical Miles resection.

Hospital deaths for all patients who underwent resection are listed in Table 2.

The one feature of surgical treatment of large-bowel cancer on which all surgeons of experience appear to be in accord is that a procedure aimed at relief that fails to remove the primary growth, except possibly in the presence of a high degree of obstruction, gives little or no alleviation. Consequently, operative procedures have become more extensive to accomplish this end. As indicated in Table 3, it has likewise been my practice to remove tissues or organs invaded by contact spread, even in the presence of liver metastasis or advanced age of the patient, the eldest being aged eighty-three years.

A critical check of the complications in any series of major procedures is often sobering, if not instruc-

tive. Such a review may yield information that will prevent the repetition of undesirable occurrences and permit the earlier recognition and treatment of others, thereby reducing morbidity and mortality. Inasmuch as it was my custom to manage the impaired bladder function incident to operative trauma by use of the inlay catheter for seven to twelve days after operation, all patients included in this survey must have had some degree of urinary-tract infection, and yet there were apparently no severe or protracted symptoms of cystitis. With two exceptions the patients were able to void with little or no difficulty at the time of dismissal from the hospital. These two irregularities and all other serious, nonfatal complications are recorded in Table 4.

The circumstance that new cancers develop and others reappear years after the initial lesion has been removed presents another aspect of the present-day attitude toward management. The

TABLE 4 Serious Nonfatal Complications in 85 Resections in 100 Cases

COMPLICATION	NO OF CASES
Urinary obstruction	2
Sloughing membrane of urethra	1
Encephalopathy	1
Retraction of colostomy stoma	1
Small bowel obstruction	4
Thrombophlebitis and embolism	2
Separation of suture line	2

success of a second resection, as recorded by Dunphy,⁷ Young⁸ and others, serves to stress the importance of a thorough examination of the patient whenever disorders suggesting cancer reappear, since long periods of arrest may follow a radical reoperation, with gratifying results to both patient and physician.

Although it has been impossible to determine in my own group of patients how many actually became victims of a recurrence or of a new cancer, both conditions were known to have occurred. One patient has remained in good health for a period of seven years after the removal of the rectal stump with its recurrent cancer, which was discovered and resected twelve months after an anterior resection and colostomy in another hospital. A second patient lived more than six years after the removal of a new sigmoidal cancer, which appeared approximately four years after the extirpation of a malignant lesion of the rectum. A Miles resection, performed on a third patient, disclosed a rectosigmoidal cancer that neither at the operating table nor on examination by a pathologist revealed lymph-node invasion. Unilateral metastatic cancer became manifest six years and three months later in the inguinal and iliac lymph nodes. The perineal and abdominal-wall tissues were free from any recurrence, urinary-tract signs and symptoms were in

abeyance, and a roentgenogram of the spine revealed nothing abnormal. On opening the abdomen I found no disease of the presacral region, peritoneum, liver or organs or tissues other than those mentioned. Consequently, the inguinal and iliac lymph nodes were resected according to the method of Taylor and Nathanson.⁹ The nodes were firm and not adherent to important structures. The largest node measured 3.2 cm. in diameter. Two years and three months later, re-examination revealed that the patient was doing manual labor at the age of seventy-three years. There had been no evidence of a local recurrence or involvement of the opposite groin, but for a month he had been annoyed by a "burning sensation" on voiding and

rectosigmoid region are presented. The pressing need for earlier recognition of this type of cancer is again emphasized. Results obtained in terms of hospital deaths and survival rates are recorded, and fatal and significant, nonfatal complications are enumerated. Success obtained from a second resection in a very limited number of patients with recurrent or new cancer is noted. Although insufficient time has elapsed since treatment of the last patient to permit determination of the final figures on five-year survivals, attention is called to the fact that the trend of the immediate post-operative hospital death rate is definitely downward.

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TABLE 5 *Survivals* among 100 Cases of Rectal and Rectosigmoidal Cancer*

Datum	No. of Cases
Radical resections	85
Patients surviving resection	77
Patients lost to follow up	0
Death in less than 5 yr.	36
Death after 5 or more yr.	5
Patients living less than 5 yr.	16
Patients living 5 to 10 yr.	16
Patients living 10 or more yr.	4

*Five-year survival rate to June 9, 1948, excluding hospital deaths was 32.46 per cent (25 cases).

a urinary frequency of two or three times nightly. Microscopical examination of tissue obtained by a transurethral resection revealed prostatic cancer. His response to prostatic revision has been satisfactory, and he continues to work.

The survival periods for the entire group to June, 1948, are summarized in Table 5.

SUMMARY

Observations on a group of 100 consecutive patients with cancer involving the rectum and

REPEATED NEPHROTIC EPISODES WITH NORMAL URINE, SERUM PROTEIN AND CHOLESTEROL IN THE EDEMA-FREE INTERVALS*

HARRY A. DEROW, M.D.†

BOSTON

A PATIENT in whom the nephrotic syndrome appeared and disappeared on three occasions has been observed from 1933 to 1948. During each remission albuminuria and edema disappeared, and the serum protein and cholesterol values returned to normal. Only 3 similar cases have been located in the extensive literature on the subject. The details of this case including the many observations made over the period of fifteen years and a review of the relevant literature are the subject of this report.

CASE REPORT

M. C. (B.I.H. No. 18029), a 17-year-old boy, entered the hospital on April 17, 1933, because of swelling of the lower eyelids and over the sacrum. Until December, 1932, he had been well except for chronic eczema of the right hand. At that time swelling of the legs developed, later, swelling of the thighs and lower eyelids and over the sacrum was noted. Except for the edema, which had continued until admission to the hospital, there had been no symptoms or history of a respiratory tract or other infection or smoky or bloody urine.

Physical examination revealed a tall, pale, poorly nourished boy with definite puffiness of the eyelids and pitting edema over the sacrum but no edema elsewhere. The fundi were normal as were the throat, heart, lungs and abdomen. The blood pressure was 104/75. Examination of the urine showed a specific gravity of 1.035 and a large amount of albumin, but the sediment was normal. During the hospital stay of 1 week the urine specific gravity ranged from 1.018 to 1.035. Additional specimens showed doubly refractile bodies and an occasional white cell and cast. Phenolsulfonephthalein excretion was 55 per cent in 2 hours and 10 minutes after the intramuscular injection of 1 cc of the dye. Examination of the blood revealed a normal non-protein nitrogen, low serum protein and serum albumin and elevated serum cholesterol values (Table 1). During a 1-week stay in the hospital the albuminuria diminished to a minimal amount, and the edema entirely disappeared. After discharge on April 25 albuminuria decreased further, finally disappearing in June.

Routine physical examination on admission to the first-year class at Harvard College in September disclosed no edema. The urine had a specific gravity of 1.020 and was free of albumin and the sediment was normal. The blood pressure was 110/70. In June 1934 the findings were the same. At that time, blood chemical studies were normal (Table 1).

On October 17 the patient was admitted to the Stillman Infirmary of Harvard University because of malaise and anorexia, which had developed without antecedent infection.† Edema of the extremities had recurred. The urine showed considerable albumin, the specific gravity ranged from 1.014 to 1.028, and the sediment contained occasional red and white cells, casts and many cells with "fat globules." Blood chemical studies were similar to those in the first episode (Table 1). Toward the end of the first week of the infirmary stay the edema disappeared. Upon discharge on November 27, the patient was free of edema but showed massive albuminuria, hypoproteinemia and hypercholesterolemia.

*From the Medical Service, Beth Israel Hospital and the Department of Medicine, Harvard Medical School.

†Associate in Medicine, Harvard Medical School, visiting physician and head of Nephritic Clinic, Beth Israel Hospital.

‡I am indebted to Dr. Alfred E. Krane of the Department of Hygiene, Harvard University, for data on the patient's condition during this episode.

During December marked edema of the eyelids, legs and sacrum recurred. Examination of the urine revealed massive albuminuria and a specific gravity of 1.024, and the sediment contained occasional red cells and casts.

He was readmitted to Stillman Infirmary from January 24 to February 1, 1935, with mild impetigo. The edema disappeared as the impetigo cleared. The albuminuria gradually diminished and finally disappeared in April.

Many examinations from May, 1935, to March, 1945, showed no edema. During this 10-year period the urine was normal except in February, 1936, when after a cold and sore throat a minimal amount of albumin and 2 or 3 red and white cells per high-power field in the sediment were noted. In May, 1937, postural albuminuria was found. In April, 1938, the patient suffered with streptococcal sore throat and in July because of acute suppurative appendicitis he underwent an appendectomy, neither of these infections was accompanied by albuminuria except for a minimal amount on the day after operation.

The serum proteins and cholesterol were normal throughout this remission (Table 1). In September, 1940, when he enlisted in the Army, and in April, 1943, when he entered officers' candidate school, urine examinations were negative.

On March 1 and 2, 1945, while overseas, he suffered with a boil on the wrist for which he was given 120,000 units of penicillin with prompt relief. Three weeks later generalized anasarca recurred. This gradually diminished with frequent intramuscular injections of mercupurin and intravenous infusions of blood plasma. On May 23 he still showed slight edema of the legs and was returned to this country. The edema of the legs persisted, and puffiness of the face and lower eyelids recurred each morning until August, when he was discharged from the Army with the diagnosis of "nephritis, chronic, glomerular, nephrotic stage, moderate, cause undetermined."

Frequent examinations of the urine during the early phase of this nephrotic episode showed massive albuminuria and erythrocytes. Massive albuminuria persisted, and the specific gravity ranged between 1.023 and 1.028. Blood chemical studies revealed hypoproteinemia, hypoalbuminemia, hypercholesterolemia and normal nonprotein nitrogen (Table 1). The blood pressure fluctuated around 120/80.

From August, 1945 to June 1948, the patient was free of edema. On August 7, 1945, examination of a single specimen revealed no albumin and a normal sediment; the specific gravity was 1.030. In January, 1946, seven consecutively voided urines collected according to a method described elsewhere‡ showed no albumin, cells or casts, the specific gravity ranged between 1.027 and 1.040. Chemical quantitation of albumin in these specimens of urine showed 3 to 7 mg per 100 cc, which is normal. At that time blood chemical studies revealed normal nonprotein nitrogen, total serum protein and serum albumin, the cholesterol was 356 mg per 100 cc. (Table 1). Physical examination was negative except for dry scaling lesions on the wrists. The blood pressure was 110/70. From June 10 to June 15, 1946, he was hospitalized because of a carbuncle of the finger, with lymphangitis of the forearm and axillary adenitis. Incision and drainage of the carbuncle and frequent intramuscular injections of large amounts of penicillin brought about prompt recovery. Examination of eleven consecutively voided specimens of urine showed no albumin, normal sediments and specific gravity between 1.006 and 1.032. Blood chemical studies were normal (Table 1). The blood pressure was 130/80. The scaling of the wrists was diagnosed as "atopic dermatitis" by a skin consultant. In September, 1947, during a follow-up visit, physical examination was negative except for a few scaling lesions on both wrists. The blood pressure was 118/70. Seven consecutively voided urine specimens§ showed no albu-

§I am indebted to Mr. William Wright, of the Medical Laboratory, John Hancock Mutual Life Insurance Company, Boston, Massachusetts, for these determinations.

min, with normal sediments, the specific gravity ranging between 1.023 and 1.028. In January, 1948, the patient was given frequent intramuscular injections of large doses of penicillin for a carbuncle on the neck, with prompt recovery. Urine examinations were not performed. Edema did not recur. In June during a follow-up visit, physical examination was negative except for very few scaling lesions on one wrist. The blood pressure was 120/80. Eight consecutively voided urines¹ showed no albumin, the sediments were normal, and the

syphilis, gold intoxication, renal-vein thrombosis,² lupus erythematosus⁴ and mercury poisoning^{3, 6}.

The course of the nephrotic syndrome in these conditions shows considerable variation. In some, edema and albuminuria disappear, and the blood proteins and cholesterol return to normal levels. In others, although albuminuria persists, the edema

TABLE 1 Summary of Laboratory Findings

DATE	NUMBER OF SPECIMENS EXAMINED*	SPECIFIC GRAVITY	ALBUMIN	URINE FORMED ELEMENTS AFTER CENTRIFUGATION (PER HIGH POWER FIELD)		
				Red Blood Cells	White Blood Cells	Casts
First nephrotic episode						
4-17-1933	3	1.020	+++ to ++++	0	0-3	0-1
to		to				
4-20-1933		1.035				
4-25-1933	1	1.018	+	0	1-2	0
First remission						
9-1933	2	1.020	0	0	0	0
to						
6-1934						
Second nephrotic episode						
10-17-1934	7	1.014	+++ to ++++	Occasional	0-8	Occasional
to		to				
2-20-1935		1.028				
3-20-1935	1	1.024	++	Occasional	Occasional	0
Second remission						
5-9-1935	6	1.020	0	0	0	0
to		to				
9-11-1935		1.028				
2-10-1936	1	1.025	+	2-3	2-3	0
2-12-1936	7	1.024	0	0	0	0
to		to				
9-9-1936		1.030				
5-19-1937	1	1.025	0	0	0	0
	2	1.015	++	0	0	0
		to				
		1.025				
6-19-1937	10	1.020	0	—	—	—
to		to				
7-22-1938		1.026				
7-23-1938	1	1.022	+	0	0	0
7-26-1938	11	1.018	0	0	0	0
to		to				
4-1943		1.030				
Third nephrotic episode†						
3-23-1945	Very frequent		++++	Positive	0	0
to						
5-15-1945	Many		++++	0		
5-23-1945						
to						
8-2-1945	5	1.023	++++	0	0	0
		to				
		1.028				
Third remission						
8-7-1945	1	1.030	0	0	0	0
1-30-1946	7	1.027	0	0	0	0
to		to				
1-31-1946		1.040				
6-10-1946	11	1.006	0	0	0	0
to		to				
6-15-1946		1.032				
9-11-1947	7	1.023	0	0	0	0
		to				
		1.028				
6-12-1948	8	1.018	0	0	0	0
		to				
		1.029				

*Examinations for sugar negative

†Postural albuminuria

‡Complete data not available from Army hospitals

§Quantitative albumin 3-7 mg. per 100 cc.

specific gravity ranged between 1.018 and 1.029. Blood chemical studies were negative.

DISCUSSION

The nephrotic syndrome is characterized by massive albuminuria, hypoproteinemia, hypercholesterolemia and edema. It occurs most often in glomerulonephritis. Other causes are lipid nephrosis, intercapillary glomerulosclerosis, renal amyloidosis,

continues with very little change, or it may decrease or even disappear for a time only to recur, it may also diminish gradually and disappear coincident with a decrease in albuminuria, development of impairment in renal function, hypertension and, later, renal insufficiency.

However, cases of repetitive nephrotic episodes with normal urine, total serum protein and cholesterol in the edema-free intervals have rarely been

observed Leiter,⁷ Fishberg⁸ and Wilson,⁹ in their wide experience with renal disease, have never observed a case of this type. In an excellent review of the literature Bradley and Tyson^{10, 11} did not describe such cases. Recently, a sixteen-year-old girl with petit-mal seizures was described¹² in whom the nephrotic syndrome appeared during the

rotic symptoms and signs to the time of writing.¹³ Addis¹⁴ recently described 2 cases in which the nephrotic syndrome appeared and disappeared on two occasions as follows:

Case B. H., female, aged 25 — Edema and proteinuria found October 1923. Both went away in the autumn of 1924, but proteinuria and later edema reappeared in 1925

TABLE 1 (continued)

BLOOD NONPROTEIN NITROGEN	TOTAL SERUM PROTEIN	BLOOD			HEMOGLOBIN	BLOOD PRESSURE
		SERUM ALBUMIN	SERUM GLOBULIN	SERUM CHOLESTEROL		
mg per 100 cc	gm per 100 cc	gm per 100 cc	gm per 100 cc	mg per 100 cc	%	
24-26	4.5	1.5	3.0	440-480	80	100/70
26	4.5	1.5	2.8			
	4.4	1.8	2.6			103/80
	6.4	4.8	1.6	154	—	110/70
	4.5	2.0	2.5	580	75	118/70
	5.5					
26-31	5.4	3.5	2.1	114-175	—	98/60 to 110/70
	5.7	4.0	1.7			
30	6.82			145-187	90	100/60 to 110/60
31-37	7.3	4.3	3.0	173-230		
	6.1					
—	—	—	—	—	94	90/50 to 123/72
					87	
27-31	7.1	4.6	2.5	166-250	80	110/70
	6.7				85	
Normal						
Normal	5.04	2.16	2.88	588		120/80
23	8.4	5.2	3.2	356		110/70
29	7.14	5.01	2.13	167	100	150/80
—					100	118/70
—	8.5	5.0	3.5	185	—	120/80

administration of tridione and disappeared upon withdrawal of the medication on three different occasions. Hypertension and microscopical evidence of hematuria were found during the second nephrotic episode, and elevation of the blood urea nitrogen to 47 mg per 100 cc was found in the third nephrotic episode. This report was published five months after recovery from the third nephrotic episode, and the patient had remained free of neph-

and continued until October 1925. No recurrence of either edema or proteinuria up to 1938.
Case P. L., male, aged 7 — Edema and proteinuria lasted for less than a month in 1935, and both disappeared. Both returned in 1938. The edema quickly went, but the proteinuria did not disappear until 1940.
In my case reported above the first two nephrotic episodes, in 1933 and 1934-1935, developed without definite antecedent cause. It is possible, however, that the first two nephrotic episodes were related

to secondary infection of the eczematous lesions. The third episode in 1945 followed a boil on the wrist, but the patient had had other infections including a streptococcal sore throat and acute suppurative appendicitis in 1938, a carbuncle on a finger in 1946 and a carbuncle on the neck in 1948 without recurrence of the nephrotic syndrome. Although the evidence does not permit one confidently to relate infection to the recurrent nephrotic episodes this possibility should be explored in patients who exhibit this phenomenon.

In the case reported by Barnett et al.¹² the findings of hypertension and microscopical hematuria in the second nephrotic episode and elevation of the blood urea nitrogen in the third nephrotic episode suggest that those episodes were due to acute glomerulonephritis of short duration and precipitated by tridione. In my case reported above there was never hypertension or nitrogen retention. The finding of minimal hematuria in the second and third nephrotic episodes may mean that these episodes were due to acute glomerulonephritis. However, in nephrosis "an occasional red blood cell in a high power field of centrifuged specimen"¹⁵ may be seen. Addis¹⁴ found by his special technic that in his patients the rate of red-cell excretion was within normal limits and that in the few cases in which abnormal numbers were found succeeding counts showed few red cells or none.

Leiter⁷ recently pointed out that "it would be easy to overlook a slight albuminuria continuing between nephrotic episodes if one did not examine concentrated urine specimens carefully." In my case presented above, repeated examinations of concentrated specimens of urine during the intervals between the nephrotic episodes and after the last episode revealed no albumin except during the second remission (Table 1). During this ten-year period, thirty-nine urine examinations were performed, thirty-five showed no albumin, whereas four showed minimal amounts of albumin under the following conditions: after a cold and sore throat, during a test for postural albuminuria, and on the day after operation for acute suppurative appendicitis. In the cases described by Addis¹⁴ "the urinary evidence of a renal lesion disappeared only to recur at a later date."

The absence of continuous albuminuria between nephrotic episodes in my case reported above and in those of Addis¹⁴ and Barnett et al.¹² is not consistent with chronic glomerulonephritis. In the latter condition, although edema may fluctuate from time to time, the albuminuria is constant and continuous. The nature of the renal lesion "that comes and goes"¹⁶ in the case reported above and in the cases of Addis¹⁴ is unknown.

The details of this remarkable case were discussed with Dr. Henry A. Christian, who states that it is unique in his extensive experience and who has presented certain aspects of the case in his recent monograph on renal disease.¹⁷

SUMMARY

The pertinent data in a patient in whom the nephrotic syndrome appeared and disappeared spontaneously on three occasions are presented. During each remission, albuminuria and edema disappeared, and the serum proteins and cholesterol returned to normal values.

The relevant literature is discussed.

520 Beacon Street

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MEDICAL MILITARY SCIENCE

MAJOR ABRAM S BENENSON, U S A *

BOSTON

DURING the past two years, a new course has appeared on the curriculum of forty-nine American medical schools. "Medical Military Science" or "Military Medicine" is its title. The Army provides its instructors, and the medical school is its sponsor. The students taking this course will shortly be members of the medical profession. That profession deserves to be informed of the training the neophyte has received in this post-war version of the Medical Reserve Officer Training Corps (ROTC).

As in the past, military medicine is an elective course offered to the student body. It is a progressive course, through the four years of medical school, meeting one hour weekly. Students are of two categories: those who are pursuing it simply as an elective course, and those who are enrolled in the Reserve Officers Training Corps. The latter must meet rigid physical standards and sign a contract at the beginning of their third year to complete the course and to attend a summer camp for training for six to eight weeks during the summer recess, after completion of the second or third year. In return, they are paid a small stipend by the Government and, on satisfactory completion of the course, are offered a commission as a first lieutenant in the Medical Corps Reserve.

The course is designed to supplement the medical-school curriculum, which prepares the student for the practice of civilian medicine. The medical school teaches him the technics involved in providing ideal medical care for the individual patient, and indoctrinates him with the fundamentals of public-health organization and practices. Military medicine introduces the student to a broader concept of mass medicine, to the problems of the situation where the facilities of standard medical practice are overburdened — in short, to the approach that must be used to cope with a catastrophe. Although it is within the realm of possibility that war will be outlawed, catastrophes will always constitute a problem in the planning of medical care. To make the material generally pertinent, the presentation is usually based on the line of action to be followed in case of catastrophe or disaster — fire, flood, blast or war.

Intelligent medical service in a catastrophe can be rendered only by planned action, with consideration of personnel densities and exposure to hazards. Medical facilities will be weighted in favor of the larger city; preparations will be made for casualties where explosive materials are stored in a burning warehouse. Conversely, the potentialities of the

situation must be known, lest the rescuers themselves become casualties. Efficient disaster relief is not spontaneous, but is dependent on prior planning and organization. The best standard for a study of these considerations is found in the Army, since its medical department is designed to cope with the catastrophes produced by enemy action.

In the first year of the course in military medicine, the organization of the Army is studied from the point of view of its effect on the disposition, number and severity of the sick and wounded. Tactics are briefly considered from the point of view of their influence, adverse or beneficial, on the problem of providing medical care. With the medical problem thus established, the over-all medical organization is taken up, demonstrating the deployment of equipment, skills and personnel to cope with the actual and potential situation, together with the integrating mechanisms (chain of command) that maintain unity of objective together with co-ordination of effort.

In his second year, the medical student is beginning his contact with clinical medicine. In his course in military medicine, it is appropriate for him to begin to consider the professional details involved in provision of medical care in disaster relief. The scheme of evacuation of the patient from the catastrophe scene, with progressions of medical care from life saving to reconstruction and rehabilitative measures as he passes through the echelons of medical care, from the aid station, through the clearing station, to the evacuation and general hospitals, is developed. The modifications in this evacuation scheme, which brings definite treatment forward to the nontransportable patient, are discussed. The contrast with routine civilian professional care becomes manifest, in that professional service is rendered to a group rather than an individual patient and that this medical care is rendered by different groups of doctors rather than by one practitioner. Maintenance of teamwork requires administrative effort at various levels. This is discussed with respect to the intramedical integration, as well as the integration of the medical aspect with the total effort. The provision of medical supplies, when the drugstore and surgical-supply house are no longer available, becomes critical. The import of available supplies in the catastrophe situation, and the necessity for standardization, procurement, stockpiling and distribution and maintenance of equipment are considered. The value of standardized equipment is demonstrated by practical sessions in the application of triangular and roller bandages, and Thomas and other stock Army splint materials.

*Professor of military science and tactics, Tufts College Medical School.

to secondary infection of the eczematous lesions. The third episode in 1945 followed a boil on the wrist, but the patient had had other infections including a streptococcal sore throat and acute suppurative appendicitis in 1938, a carbuncle on a finger in 1946 and a carbuncle on the neck in 1948 without recurrence of the nephrotic syndrome. Although the evidence does not permit one confidently to relate infection to the recurrent nephrotic episodes this possibility should be explored in patients who exhibit this phenomenon.

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room is actually demonstrated, and culminates in a field exercise in which the students participate in the evacuation and simulated field medical treatment. The many veterans among the current medical classes find this type of training reminiscent of unpleasant combat experience, and, although the objective is radically different, the similarity to previous experience suggests to them unnecessary repetition. There is discussion on the advisability of converting this summer training from field-type to professional-type training, during which the student will learn the administrative and technical

factors involved in actual medical and surgical care of the Army sick and wounded.

Those who teach this course believe that the new physician who has completed a course in military medicine is that much better a physician. He is prepared to take a leading position in community defense plans, he is prepared to serve his country in or out of the armed force. He has demonstrated his willingness to make a sacrifice for the privilege of citizenship. It is possible that he will not be as adroit in litter drill as his father, but he is that much better a citizen and physician.

MEDICAL PROGRESS

ANTIBACTERIAL CHEMOTHERAPY (Continued)*

AVRAM GOLDSTEIN, M D †

BOSTON

Resistance

Priority for demonstration of the resistance of micro-organisms to specific drugs goes to Ehrlich,^{153 155} who was able to isolate strains of trypanosomes resistant to three distinct drug classes. Resistance, in his experiments, was shown to arise by repeated passage through low concentrations in vitro or in vivo, to be permanent once established and to be specific for each class of drug. Thus, organisms made resistant to triphenylmethane dyes remained sensitive to azo dyes and organic arsenicals.

Ehrlich foresaw that drug fastness was to prove a major clinical stumbling block and proposed the only two means available for avoiding the difficulty to eliminate *all* organisms as rapidly as possible, and to take advantage of the absence of cross-resistance by employing, when possible, drug combinations.^{1 154} The same conclusions are, of course, repeatedly arrived at today from studies based upon a far more advanced understanding of the nature of resistance.

Resistance to the antibacterial chemotherapeutics was first encountered on an important clinical scale after a few years of sulfonamide treatment of gonorrhea.^{156 159} A sharp drop in the cure rate was accompanied by the isolation of increasing numbers of sulfonamide-resistant gonococci.^{160 163} Subsequent experience, both in the laboratory and in the clinic, showed that drug-fast organisms regularly developed when an initially sensitive strain was grown in the presence of an antibacterial drug. This was true with the sulfonamides and penicillin,

but the most frequent and extreme cases of resistance occurred with streptomycin.¹⁶⁴⁻¹⁶⁹

Most workers are agreed that the development of resistance, like the chemotherapeutic action itself, is quite independent of the host. *It is not the patient but the bacteria that, under certain circumstances, become refractory to further chemotherapy.*

Resistance is encountered in two distinct forms. On the one hand a variety of bacterial species are relatively insensitive to the action of any one drug, and even among sensitive species more or less resistant strains are found. Detection of such resistant strains requires the use of very large inoculums, the drug then favoring survival of the less sensitive organisms.¹⁷⁰ One of the real disadvantages of streptomycin is the very wide range of sensitivity to its action displayed by organisms of every species.

On the other hand it has been frequently shown that resistant forms may arise *de novo* during contact of organism with drug. It was long an open question whether resistance of this kind arose through spontaneous mutation during the period of contact ("current mutation") or was to be attributed to a specific interaction of drug with bacteria. The outstanding work of Demerec¹⁷¹ now appears to have settled the question in favor of the former hypothesis, at least for *Staphylococcus aureus* and *Escherichia coli*. Mutations occurring in random fashion give rise to resistant variants, which are then favored by selection in the presence of a drug. Resistance to penicillin and the sulfonamides proceeds stepwise with selection at each step to yield populations of higher and higher degrees of resistance.^{78 165} This is explained by the postulated presence of several genes, mutation of any one pro-

*From the Department of Pharmacology, Harvard Medical School.
†Associate in pharmacology, Harvard Medical School.

This is combined with instruction in the practical first-aid measures that a second-year medical student should have in his armamentarium.

The catastrophe situation fosters the development of disease. In earlier wars the problems produced by disease and epidemic have exceeded medical capacity. In the last two years of the course, the advances of military preventive medicine that were successful in avoiding this eventuality in the recent war are presented. The methods that the Army has found of value in following the disease situation and in forestalling epidemics are discussed. Military preventive medicine encompasses all sanitary situations, from the most hazardous to the most salubrious, from the frozen Arctic to the tropical jungle. The student is indoctrinated with the basic principles involved in disease prevention and, guided by methods that have been found successful, is taught to improvise the solution fitting the particular situation in which he may find himself. The necessity and the means of enforcing the most rigid sanitary control in the catastrophe situation are stressed.

In these clinical years, while orthodox medicine, surgery and psychiatry are being presented, military medicine presents the modifications induced by the catastrophe situation. Therapy must be projected spatially as well as temporally. The teamwork impelled by the echelon system of medical care requires standardization of therapeutic procedure. Although the practice is repugnant to the traditionally individualistic physician, the welfare of the patient requires a limitation of procedures based on availability of equipment and personnel and the exigencies of the local situation. The concept of teamwork dictates that the plays be called in advance and that one man carry the ball just so far, passing it to his teammates who have been prepared to carry on. In medicine and surgery, the objective is the civilian ideal medical care. However, the disaster situation will often force the results to fall short of that objective, since masses rather than individuals are concerned, in the field rather than a scientifically designed operating theater. Still the recent war produced a medical record of which no member of the profession need be ashamed.

The psychiatric picture in the catastrophe situation is distorted by the disruption of normal habits, normal gratifications and psychic supports. The emotionally unstable may well be driven from the normalcy they cling to. The need for and value of preventive psychiatry and the feasibility of very early and mass therapeutic measures are demonstrated.

There are in addition unusual health hazards with which the military authorities are primarily concerned. Although diplomats may strive to eliminate the need, the medical profession must still be prepared to cope with the catastrophe produced by

nuclear fission and chemical agents—a continual threat by accidents, industrial or diplomatic. The medical management of these situations is discussed in the fourth year.

It may be seen that the medical ROTC course today is primarily professional. This is consistent with current military planning, in which emphasis is placed on the professional qualities of medical personnel. However, the student who completes this course is to be qualified to assume the position of a commissioned officer in the Army. To this end, a minimum of time is devoted to give the future medical officer enough knowledge to avoid the embarrassment experienced by many medical officers who received their commissions with no military training and entered active duty with the relatively high rank conferred on all medical officers. The ROTC student is taught to recognize the grade insignia of personnel of the armed forces, he is also taught the principles of military courtesy and command and of military law. The basic principles of military correspondence and administration are explained, dispelling the physician's impression of "red-tape." He is given enough instruction in map reading to provide terrain appreciation and orientation—a knowledge of practical value.

As a potential member of the Army Medical Department, he is instructed in what it has to offer him. Its history and evolution to its present pattern and what it has contributed to the knowledge of medicine are discussed. Its research methods and plans, the part each person plays in contributing to the store of knowledge by keeping medical records is explained, and what the services offer as a medical career are discussed.

The history of this country shows that the medical profession has been outstanding in its patriotism. Traditionally the doctor is an "educated" man, not only professionally but also generally. However, the medical student of the current day has rarely the time to ponder the problems that confront the country. In the course in military medicine, three hours during each year are devoted to a discussion of the currently confusing and difficult problem of national and international affairs, reminding the student that, even while he is in medical school, he still has obligations to his country.

The medical ROTC program has completed its first year at Tufts College Medical School. Despite a student body composed largely of veterans, there has been a real and increasing response to the program. Student comment has indicated that the participants in the program concur in the practical value to be obtained from such a course. One third-year student wrote, "This course should be 'advertised' as essential to freshmen."

Present summer-camp attendance required of enrolled students consists of a six-week period of training at Fort Sam Houston, Texas, during which the material covered in the medical-school class-

small animals (such as the mouse intravenous LD_{50}), chronic reactions are brought out by prolonged feeding or repeated injection into a variety of animals. Molitor's¹⁹¹ report on streptomycin is a classic study of acute and chronic toxicity in animals.

Unfortunately, as Marshall¹⁹³ points out, although animal toxicity may in a general way resemble effects in human beings, the correlation is by no means reliable, and toxic dosage, expressed in milligrams per kilogram, can rarely be translated from species to species. The wartime antimalarial program¹⁹⁴ brought this out for a considerable number and variety of drugs. Furthermore, reactions of the sensitivity type often cause the greatest difficulty in the clinic, and yet these are rarely observed in experimental animals. Caution is therefore necessary in the prediction of human toxicity from animal experimentation alone, although without question major toxic potentialities will be revealed in such studies.

Sulfonamides Sulfonamides display a variety of untoward effects, manifested by sulfadiazine and sulfamerazine to a lesser degree than by some of the earlier members of this group. These have been fully discussed by Janeway.¹⁹⁵ The major toxic manifestations of sulfathiazole, sulfadiazine and sulfamerazine are damage to the kidneys, interference with the normal production of leukocytes, and fever. The last two are evidently sensitivity phenomena, unpredictable, and often elicited by extremely small doses. The prevention of granulopenia has not been achieved, but the gravity of this condition has been considerably minimized by prophylactic control of secondary infection with penicillin.

The twofold effect upon the kidneys (crystalluria and toxic nephrosis) is closely dependent upon the drug dosage and certain other important factors. Crystalluria has long been recognized as a simple consequence of supersaturation of the urine, where these drugs and their acetylated derivatives are highly concentrated. All become increasingly soluble at an alkaline pH, a fact that provides the rationale for adjuvant alkalization, forcing of fluids to permit excretion of a reasonably dilute urine and frequent check on the urine pH and specific gravity. An interesting approach to this problem was proposed by Lehr¹⁹⁷ and also by Frisk and his co-workers,¹⁹⁸ who demonstrated that, as theory predicted, the solubility of one sulfonamide is almost independent of others present in the same solution — for example, a saturated solution of sulfathiazole will dissolve nearly as much sulfadiazine as an equal volume of water. It had long been known that most of the sulfonamides act similarly, and more or less additively against sensitive microorganisms. These facts are the basis of the suggestion that mixtures of sulfonamides invariably be employed, whereby the total dose is divided among three drugs. The mixture employed by Frisk, with

significant reduction in crystalluria, consisted of sulfathiazole, sulfadiazine and sulfamerazine in the proportions 37:37:26. Larger doses could be given and higher blood levels (of total sulfonamides) attained than otherwise, without supersaturating the urine with any of the three compounds or their acetyl conjugates. Whereas crystalluria is unquestionably reduced in experimental animals,¹⁹⁹ and in some clinical experiences,²⁰⁰ conflicting clinical reports have appeared.²⁰¹ One might raise the question whether it is wise to risk sensitizing patients to three drugs instead of one in view of the fact that patients reacting to sulfathiazole, for example, often tolerate sulfadiazine or sulfamerazine. Whether from the standpoint of over-all toxicity the use of mixtures is in fact superior to single-drug regimes remains to be proved in a statistically valid number of patients.

It is not clear whether the toxic nephrosis occasionally seen is closely related to the crystalluria, but, curiously enough, alkalization of the urine reduces the incidence of both.²⁰²

Penicillin Penicillin remains a pharmacologic curiosity because of its almost completely innocuous character. No toxic effects of the dose-related type have been reported, this is the more remarkable in view of the enormous number of persons (literally millions) who have received the drug. The lethal dose of penicillin cannot be determined since it is less toxic than any of the cations (sodium, potassium, calcium and so forth) with which it has been associated.²⁰³ Doses of several million units daily are regularly tolerated in the treatment of refractory diseases, but it must be observed that the "enormous" dose of 10,000,000 units daily represents only 6 gm of penicillin G sodium, and only 0.5 gm of the cation. On the other hand intrathecal injection may, and direct cortical application does, lead to convulsive phenomena of unknown mechanism with both penicillin²⁰⁴ and streptomycin.²⁰⁶

Sensitivity reactions occur in about 5 per cent of patients, usually as urticaria (which responds to antihistaminic drugs), dermatitis or drug fever.⁶¹ These appear most frequently with oil-and-wax mixtures, which are also prone to cause annoying local tissue reactions.²¹²⁻²¹⁴

Streptomycin Streptomycin, unfortunately, displays a serious toxic effect of the dose-related type — that upon the eighth nerve and vestibular apparatus.²¹⁵⁻²¹⁸

The relative infrequency of this injury in the therapy of acute infections suggests that duration of therapy (or total dose) is the crucial factor. The statistical incidence of the reaction is not easily assessed, since it often appears in mild and reversible form as a disturbance of hearing or equilibrium that may not be especially prominent while patients are bedridden.²¹⁵ Moreover, a number of the reported cases occurred in persons suffering from

ducing about the same degree of resistance and successive mutations producing additive effects. Since a double mutation would be an extremely improbable event, Step 1 mutants become predominant before a second mutation results in establishment of Step 2 mutants, and so on. With streptomycin, however, the stepwise character is by no means regular, variants of extremely high resistance may arise at once from a sensitive parent strain.^{165 166 172} This fact is explained by the assumption that the several genetic factors vary in potency, since chance alone determines which will mutate, the result is an unpredictable irregularity in the degree of resistance. It follows that, with sulfonamides and penicillin, resistance can be controlled by reduction of the total number of growing organisms (since cell division favors mutation probability) to lower thereby the possibility of a Step 1 variant mutating again to Step 2. With streptomycin this is practically impossible since the first mutation of a sensitive organism may yield a highly resistant offspring. (A general review of the mutation problem was presented at the Cold Spring Harbor Symposium of 1946.¹⁷³)

Several investigators have shown that resistance only develops in actively growing populations,^{164 172 174} as one would expect on theoretical grounds. One type of resistance to penicillin, characterized by production of penicillinase, may be increased *pari passu* with a rise in penicillinase activity, by rapid growth and frequent subculture in the absence of the drug.¹⁷⁴ Grown in ordinary mediums in the absence of penicillin, such resistant organisms do not revert, but when they are supplied with special substrates, reversion to the previously sensitive condition occurs.¹⁶² It has never been shown that penicillinase meets the criterion for an adaptive enzyme, but exactly analogous findings regarding the appearance and disappearance of adaptive enzymes have been reported by Spiegelman and Reiner.¹⁷⁵ A theoretical approach to drug resistance, with emphasis on adaptation, is advanced by Hinshelwood,¹⁷⁶ and a conflicting point of view is presented by Sevag.³⁷

A study of streptococci of groups A, B and C, grown in penicillin, reveals that one bacterial group may differ from another of the same species, in the tendency to become drug-fast, the characteristics of the resistant forms and the permanence of resistance.¹⁷⁷ Resistant organisms arising through current mutation sometimes show a surprising tendency to revert upon removal of the drug,¹⁰¹ this is difficult to explain on a basis of back-mutation unless it can be shown why nonresistant forms would be favored in the absence of drug. The only evidence bearing on this is the finding that certain resistant strains have a slower growth and metabolic activity than the parent sensitive strain.^{78 104}

Except for the unique case of penicillinase-producing organisms, it is now generally accepted

that bacteria become drug-resistant by developing an alternate metabolic pathway, which by-passes the previously inhibited steps. How this could occur on a mutation basis is indicated by the fundamental studies of Beadle and his collaborators,¹⁸¹ who showed that the presence or absence of the enzyme mediating each metabolic step in *Neurospora* is controlled by a single gene. Appearance of a new enzymatic step circumventing that inhibited by a drug might thus arise from random gene mutations. Of unusual interest in this connection is the report of a *Neurospora* variant requiring sulfonamide for growth and inhibited competitively by PABA.¹⁸²

From the clinical standpoint the resistance problem offers the greatest drawback to the use of streptomycin. It has been shown repeatedly that organisms cultured from refractory patients after prolonged therapy prove resistant as compared with the original strain and that this development may occur with alarming rapidity,¹⁷⁹⁻¹⁸⁴ often carrying a disease quickly beyond control by the drug. This emphasizes the importance of frequently determining organism sensitivity and, so far as possible, increasing dosage to meet new thresholds.

If the concepts outlined above are correct there seems no sure method of avoiding drug fastness. "Frappier fort et frapper vite"¹⁸⁵ remains the only countermeasure. Mutation to resistance is unlikely to occur if multiplication of organisms can be stopped at once, and variants beyond the first step will almost certainly not appear. Prompt treatment with adequate dosage until an infection is entirely eliminated offers the best hope of control. Combined medication, suggested by some authors¹⁸³ and yet not generally employed, seems thoroughly logical since the few variants resistant to one agent can be controlled by the other before selection makes them the predominant type.

The appearance of streptomycin-requiring organisms has been reported by several investigators.¹⁸⁶⁻¹⁹⁰ These were avirulent for animals until streptomycin was administered, when fatal infection promptly ensued. Although it is not inconceivable that these facts may have clinical significance, the results cited were obtained *in vitro* and no authenticated case of therapeutic failure on this basis has yet been reported.

TOXICITY

It is axiomatic that an effective chemotherapeutic is a compound of low toxicity that has shown a favorable chemotherapeutic ratio in experimental animals. Toxicity, broadly speaking, is of two kinds: one bears a definite relation to dosage, the other falls into the category of sensitivity phenomena, whose incidence and severity do not strictly depend upon the amount of drug administered. Either type may appear after brief or prolonged exposure to a drug. Acute reactions of the first kind are generally elicited in toxicity tests with

against infection when the animals were injected with pneumococci *after disappearance* of detectable plasma levels following a single dose of penicillin. This result may be explained in part by the recent findings^{233, 234} that penicillin levels in tissues and lymph persist for some time after plasma levels have disappeared.

In human beings gonorrhea has been cured by a single 15-mg dose of penicillin,²³⁵ and prevented by the single prophylactic administration of 1 or 2 gm of sulfathiazole.²³⁶ The meningococcus carrier state can be eradicated by a single dose of sulfadiazine.²³⁷

These observations must all be interpreted in relation to the duration of levels after the single

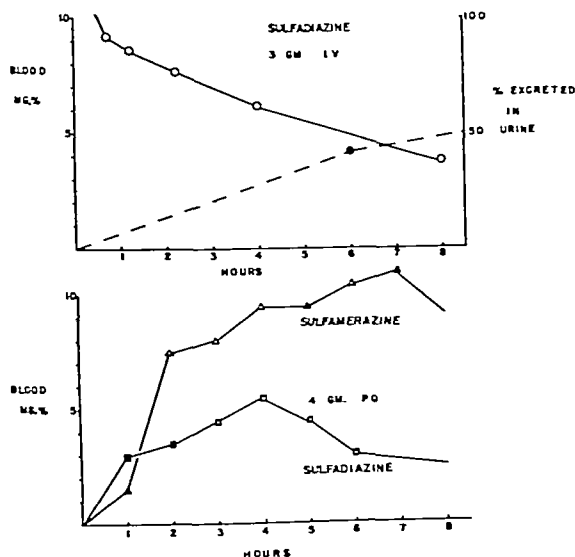
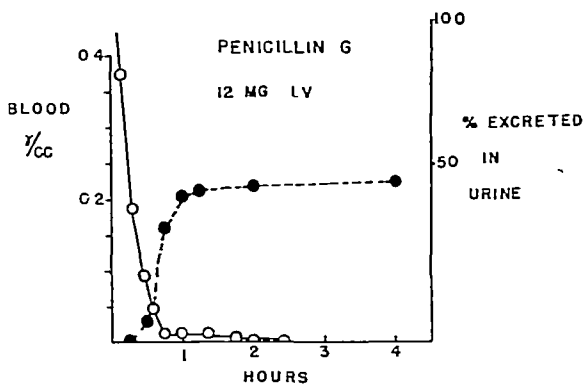


FIGURE 4

The upper half shows blood levels (solid curve) and cumulative urinary excretion (broken curve) of sulfadiazine after single intravenous administration (data of Sadock and Tredway²³³). The lower half shows blood levels of sulfadiazine and sulfamerazine after single oral administration (data of Bullock and Ratish²³⁹).

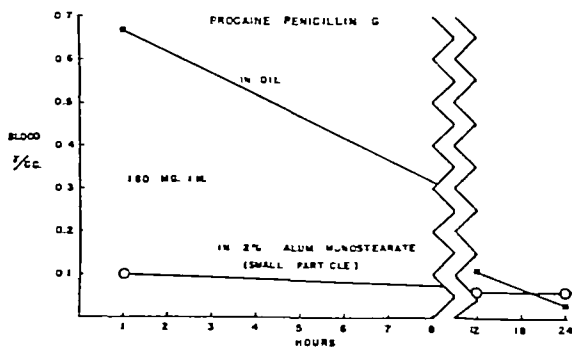
dose, the threshold level for the organism concerned and the response of the organism to varying periods of exposure to the drug. Every "single dose" is in reality a *course of treatment*, in which the pathogens are exposed to a changing drug level for a definite period (Fig 4-6). Increasing the size of the single dose not only raises the peak level but also prolongs the duration of suprathreshold concentrations. If an infection can be cured by short exposure of pathogens to a low drug concentration, effective cures will also, of course, be obtained through a wide range of higher doses and longer exposures. The experiments cited, then, represent a critical testing of the minimal requirements for cure, in infections caused by highly sensitive organisms.

Refractory infections provide a more exacting test of the limits within which dose and frequency can be varied. In the treatment of subacute bacterial endocarditis, Loewe²⁴² reports that patients who fail to respond to prolonged therapy by the

FIGURE 5 Blood Levels (Solid Curve) and Cumulative Urinary Excretion (Broken Curve) of Penicillin G after Single Intravenous Administration (Adapted from Data of Rammelkamp and Keefer²⁴⁰)

continuous route at a constant plasma level may be cured when the plasma penicillin level is raised. Priest and his collaborators²⁴³ also stress the importance of high and constantly maintained plasma levels in the management of this disease.

The fundamental studies of Eagle and his associates²⁴⁴ on time-dose relations in the cure of rabbit syphilis, demonstrate clearly that therapeutic efficiency depends upon maintenance of an effective blood penicillin level for a specified period of time.

FIGURE 6 Penicillin Blood Levels after Single Intramuscular Administration of Two V.E.R. Repository Products (Data of Thomas et al.²⁴¹)

The dose curing half the animals (CD_{50}) was lowest when repeated injections of small amounts of penicillin were given for a long time. The lowest CD_{50} was 360 units per kilogram of body weight, given as fifty injections (7.2 units per kilogram each) at

infectious disease of the central nervous system so that the drug could not surely be implicated. In any event the tendency has been, when possible, to avoid administering streptomycin for longer than a few weeks.²¹⁹ In the treatment of chronic infections analogy to the arsenicals might suggest rest periods, but this is illogical because it would favor the development of drug resistance. The problem appears to lack a practical solution, the nature of the remarkable specific affinity for a particular group of nerve cells²²⁰ is not understood, and the clinician is left little choice but to weigh the risk of prolonged treatment against its possible value and to warn the patient of the hazard.

In the therapy of urinary-tract infection, which constitutes one of the major indications for streptomycin, advantage should be taken of the enhanced potency of the drug in alkaline solution, chemotherapy should be preceded and accompanied by alkalization procedures.²²¹ By increasing the potency of each microgram of streptomycin excreted into the urine one is enabled to reduce the systemic dosage to a point where the dangers of toxicity are distinctly lessened.

The use of streptomycin is also attended by the usual variety of sensitivity reactions,²¹⁸ including contact dermatitis among physicians and nurses who handle it frequently.²²²⁻²²³ Sensitivity may be ascertained by patch tests or intradermal inoculation, caution is indicated in the latter procedure by the report of a recent nearly fatal case in a hypersensitive person.²²⁴ One might observe that sensitivity reactions to drugs in general are among the least understood subjects in pharmacology. Though neglected in the past, they comprise a potentially fruitful field for joint study by pharmacologist, immunologist, physical chemist and clinician.

PHARMACODYNAMICS

Question of Drug Levels

It is generally agreed that the practical aim of chemotherapy is to administer a drug in such a way that optimal in vitro concentration will be maintained at the locus of infection, continuously and until infectious organisms are entirely eradicated. This implies that all measures employed will be designed to maintain an effective drug level in close contact with the bacterial cells.

Recently the importance of drug levels, especially in the plasma, has been questioned, particularly by Marshall.¹⁹³ That certain infections can be cured despite undetectable or negligible blood levels is undeniable, especially with drugs that are selectively taken up or irreversibly bound by parasite or tissue proteins. In the arsenic-bismuth treatment of syphilis, for example, cure is more dependent on total dose than on concentration, and the frequency of

administration is not highly critical.²²⁵⁻²²⁶ Likewise, in antimalarial therapy, some drugs are so highly concentrated in certain tissues that plasma levels are insignificant by comparison¹⁹⁴; yet even with quinacrine, which has a high tissue-plasma ratio, Shannon²²⁷ found good correlation between plasma levels and clinical response. Certainly, no generalization will apply to all drugs, the question here is to what extent plasma drug levels are important in antibacterial chemotherapy.

Little doubt has been expressed that the sulfonamides act at a definite threshold concentration determined by the sensitivity of each bacterial strain and species, and the same observation is true of the *bacteriostatic* action of penicillin and streptomycin. Eagle and Musselman⁷²⁻²²⁸ recently demonstrated a paradoxical effect whereby certain streptococci and staphylococci show a *decreased death rate in vitro* at very high penicillin concentrations. It was suggested that too much penicillin might prove harmful in infections caused by these organisms. However, the clinical importance of the "paradoxical phenomenon" can be questioned, since bacterial growth is presumably inhibited through the whole range of concentrations in which the paradoxical *bactericidal* effects are observed.

Some early workers cited the increased sensitivity of growing cells to the killing action of penicillin as a rationale for giving the drug intermittently, levels would fall repeatedly, and the bacteria would enjoy brief periods of growth, during which they would again be subject to the bactericidal effect of the drug. Here again, the importance of bacteriostatic action was overlooked. To release a dangerous pathogen from effective growth inhibition so that it can multiply and be killed is like releasing a petty criminal from jail in the hope that he will commit murder and become subject to electrocution.

Actually, the argument was *post hoc* reasoning in an attempt to explain why intermittent injection, with zero plasma levels for about half the time, was so outstandingly successful in the control of clinical infection. It has been shown that organisms removed from exposure to penicillin do not actually resume growth for several hours⁷⁴⁻⁷⁶ — a fact that goes far to explain the efficiency of an intermittent schedule.

Sweeping generalizations are sometimes made on the basis of the fact that in animal or human infection it is often possible to reduce the frequency of administration of a chemotherapeutic without loss of efficiency. For example, pneumococcal and other infections in mice have been cured by a single large dose of penicillin in place of repeated smaller doses.²²⁹⁻²³⁰ Similarly, guinea pigs can be protected against lethal tuberculous infection if streptomycin is administered as a 25-mg dose, whether that amount is given daily, or once in five days.²³¹ In a well designed experiment²³² rats were protected

against infection when the animals were injected with pneumococci *after disappearance* of detectable plasma levels following a single dose of penicillin. This result may be explained in part by the recent findings^{232, 234} that penicillin levels in tissues and lymph persist for some time after plasma levels have disappeared.

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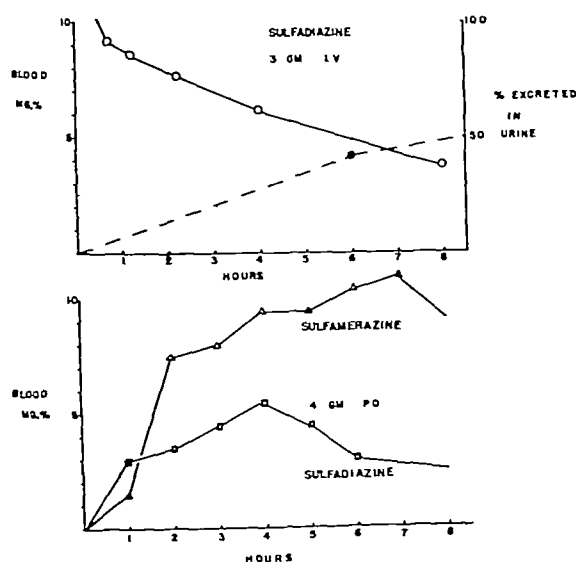


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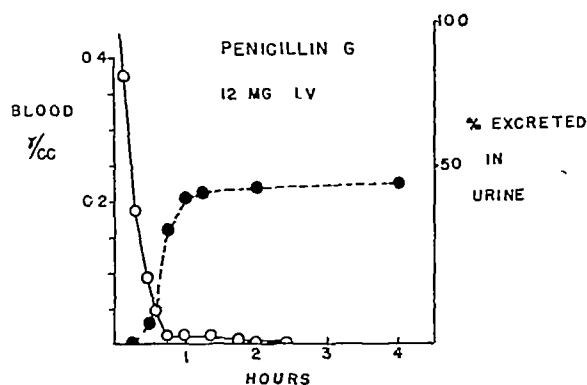


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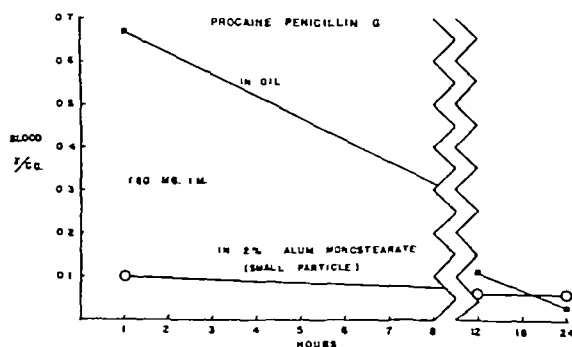


FIGURE 6 Penicillin Blood Levels after Single Intramuscular Administration of Two New Repository Products (Data of Thomas et al.²⁴⁵).

The dose curing half the animals (CD_{50}) was lowest when repeated injections of small amounts of penicillin were given for a long time. The lowest CD_{50} was 360 units per kilogram of body weight, given as fifty injections (7.2 units per kilogram each) at

four-hour intervals. Increasing or decreasing the interval, or reducing the number of injections with the same interval, had the effect of raising the CD_{50} — that is, more penicillin was required for cure.

The clinical counterpart of these studies is embodied in the report of Schwemlein et al.²⁴⁶ on the results of penicillin therapy of syphilis, with and without artificial fever, in large groups of patients treated according to different schedules. The results, which confirm the synergistic action of artificially induced fever, are also pertinent to the present discussion. Assuming the various treated groups to be comparable, the data have been tested for statistical significance, with the following results: when a total of 720 mg (1,200,000 units) was administered over one and a fourth and seven and a half days (both groups with accessory fever) to patients with primary syphilis, there was no significant difference in the cure rate, comparison of the same schedules in patients with secondary or relapsing syphilis gave a marked advantage to the longer schedule. It is obvious, as had previously been recognized, that early syphilis responds more easily than the longer established types. In such easily eradicated infections both the dose and the duration of treatment were probably more than adequate even in the one-and-a-fourth-day schedule.

Examining the combined cure rates for primary, secondary and relapsing cases, one finds that the 720-mg schedule is equally effective whether spread over seven and a half or three and three-fourths days but produces fewer cures when the length of treatment is cut to one and a fourth days. Furthermore, although 15 gm is more effective than 6 gm given in a single day, it is distinctly less curative than 720 mg over three and three-fourths days. Comparing doses given over the same seven-and-a-half-day period, there is a progressive decline in the cure rate from 720 to 180 mg.

These results refute the hypothesis that cure depends largely on the total dosage, regardless of the duration of treatment. Repeated small doses, sufficient to maintain fairly constant effective blood levels for three and three-fourths days, proved more effective than twenty times the same total dose administered in a single day. The data suggest that, provided a certain minimum blood level and duration of treatment are exceeded, treponemas can be reliably eradicated within a considerable range of reciprocal variation in both these factors.

Critical re-examination of the need for constant plasma levels has contributed to knowledge of actual minimum chemotherapeutic requirements in human disease. This is especially important in the use of streptomycin, excessive administration of which causes an unnecessarily high incidence of toxicity. This drug may be given less frequently

and in shorter courses than had been thought necessary without reduction of cure rate in a number of infections.²⁴⁹

Nevertheless a wholly negative attitude toward plasma levels does not seem justified. The whole body of in vitro evidence showing the intimate dependence of growth-inhibition and killing rates upon drug concentration cannot be dismissed, nor should the established dangers of inadequate levels be overlooked in the search for the dosage schedule that will just exactly cure. Unless the immediate environment of the pathogenic organisms can be sampled (as in the urinary-tract infections) the plasma level remains the only indication of the probable drug concentration to which they are exposed.

Maintenance of Drug Levels

The establishment and maintenance of an effective drug level depends upon the following factors: dosage, and frequency of administration, rate of absorption from the drug depot, wherever established, rate of drug inactivation, if any, within the body, extent of binding to plasma and other tissue proteins, and rate of excretion. Ideally, a chemotherapeutic should be slowly but completely absorbed by the oral route, not appreciably inactivated in the body, and slowly excreted. It should not be bound to nontarget* proteins to an extent that would reduce its free concentration below that desired. Pharmacodynamic properties may be improved by independent variation of any of the above factors toward the ideal, thus, absorption may be slowed, excretion blocked, and so on.

Sulfonamides

The sulfonamides present no serious pharmacodynamic problems. Sulfamerazine comes close to the ideal in all respects, oral administration of a 1-gm maintenance dose every six to eight hours proving adequate to maintain a fairly constant bacteriostatic level of the order of 8 mg per 100 cc, and sulfadiazine, requiring ingestion every four or six hours, is not inconvenient, although levels will fall during the night if medication is stopped. Large priming doses are needed with all the sulfonamides to establish a higher plateau level than could be reached by simple repetition of the maintenance dose from the start.^{195 238 239 246-250} Figure 4 shows (upper portion) the rate of disappearance of sulfadiazine from the plasma after intravenous administration and its simultaneous appearance in the urine. The lower portion of Figure 4 shows the typical course of the plasma-level curves for sul-

*Proteins of various tissues including the plasma in contradistinction to those of the parasite.

fadiazine and sulfamerazine after *oral* administration

High local concentrations in the gastrointestinal tract are made possible through molecular modifications resulting in decreased absorption (sulfaguanidine and sulfathiadiazole²⁵¹) or very slow release of active drug (sulfasuxidine and sulfathalidine). High levels for combating localized infection in the urinary tract are automatic, so to speak, even when dosage is small and blood concentrations low, by virtue of the quantitative excretion of these drugs by the kidneys. A number of new sulfonamides have been investigated,²⁵²⁻²⁵⁵ and some whose chief virtue is high solubility have been tested in the clinic.²⁵⁶⁻²⁵⁷

Penicillin

Penicillin presents the problem of poor absorption by mouth, rapid absorption from intramuscular depots and an extremely rapid renal excretion, resulting in fluctuating levels with high peaks and deep valleys.^{240-253, 259} Figure 5 illustrates the rapid disappearance of penicillin from the plasma after intravenous administration and its simultaneous appearance in the urine. To overcome these serious deficiencies and devise some means of maintaining fairly constant levels with a modicum of comfort to the patients has been the aim of considerable research. It was early shown that oral administration of three to five times the usual intramuscular dose would yield comparable levels.²⁶⁰⁻²⁶¹ The belief that gastric acidity was largely responsible for inactivation by the oral route has been generally discarded for lack of evidence,²⁶² and simple administration every three hours of at least 60 mg (100,000 units) by tablet proves effective, though uneconomical. Results of treatment by this route of several hundred cases of gonorrhea compared favorably with those generally obtained when penicillin is given intramuscularly.²⁶⁰ The oral route, however, is contraindicated in the treatment of serious infections because absorption is, at best, irregular and unpredictable.

Early efforts were directed toward slowing absorption from an intramuscular depot by such crude means as chilling the site or injecting epinephrine, but the first method generally employed was the intramuscular injection of a large amount of penicillin in a mixture of peanut oil and beeswax (Romansky).²⁶³ A single dose of 180 mg (300,000 units) produces detectable levels for as long as twenty-four hours.²⁶⁴ The injections, however, may be painful and lead to a higher incidence of local and allergic reactions than with aqueous solutions.²¹²

The principle embodied in the peanut-oil-beeswax mixtures has led to the development of several other so-called "repository" products.²⁶⁵⁻²⁶⁶ Loewe²⁶⁷ obtained results that compared favorably with the Romansky formula, using a water-soluble

preparation of penicillin in gelatin and dextrose. It was reported that a large number of insoluble metallic salts of penicillin released the active drug at a slow rate from intramuscular depots,²⁶⁸ and complexes with cationic dyes had the same effect. A compound consisting of a mol of penicillin combined with a mol of procaine was shown to act similarly. This material, which is now on the market in several forms, when suspended in an oily vehicle, was shown to produce detectable levels for longer, and in a higher proportion of patients, than the Romansky formula.²⁶⁹⁻²⁷⁰ Herrell and his associates,²⁷¹⁻²⁷² employing procaine penicillin suspended in sesame oil, report reliable prolongation or levels up to thirty hours after a single 180-mg (300,000 units) injection. These investigators express the view that the procaine confers an anesthetic effect²⁷³ and also, presumably, an antihistaminic one, since allergic reactions are so rare, even among patients previously reacting to ordinary penicillin. Similar results have been obtained by other workers,²⁷⁴ with aqueous suspensions of procaine penicillin. In a well controlled study of six repository products, Thomas and his collaborators²⁴¹ have shown that the most favorable results are obtained with procaine penicillin in peanut oil with aluminum monostearate. The particle size is critical, a striking advantage of 5-micron over 50-micron particles being observed. With the small particle size a single injection of 180 mg resulted in levels above 0.018 microgm (0.03 units) per cubic centimeter in 86.7 per cent of the subjects after four days. Figure 6 shows the markedly prolonged plasma levels resulting from the single administration of two different repository preparations by the intramuscular route.

It should be clear that the repository method will be satisfactory for the treatment of infections requiring relatively low penicillin levels. Unfortunately, the stress that is placed upon duration of detectable levels directs attention away from the shape and height of the plasma-level curve during the whole period between injections. With the earlier repository preparations peak levels were rather low so that in grave infection requiring a high penicillin level it was more reliable to depend upon intermittent aqueous injections or continuous intramuscular or intravenous infusion. The latter method carried with it the difficulty of local phlebotrombosis, but the assurance of an unvarying, high plasma level.²⁷⁵ Thrombosis is attributed to thromboplastic effects of the drug *in vitro*,²⁷⁶ but this has been disputed.²⁷⁷ It is too early to say whether the favorable properties of the newer repository preparations will allow one to establish and maintain *high* constant levels, but this seems a likely possibility.

In the treatment of localized infections much may be gained from a local drug level higher than would result from simple equilibrium with the

plasma. Such levels can be established in infections of the skin,²⁷⁸ oral and other mucous membranes,²⁷⁹ paranasal sinuses, pulmonary tree, and other sites, by direct topical application. An interesting development along these lines is the use of aerosol or dust inhalations of small-particle size in the treatment of pulmonary, tracheobronchial and sinus infections.²⁸⁰⁻²⁸⁶ Concentrations thus established in the pulmonary tissues of animals are several times higher than those in the plasma.²⁸⁷ On the other hand the finding of definite plasma levels after aerosol or dust therapy qualifies the method as a convenient and generally useful one in systemic penicillin therapy. High drug concentrations in the urine are again attained willy-nilly as a consequence of the rapid quantitative excretion of penicillin by the kidneys.

Another approach to the maintenance of constant plasma levels has taken the obvious direction of

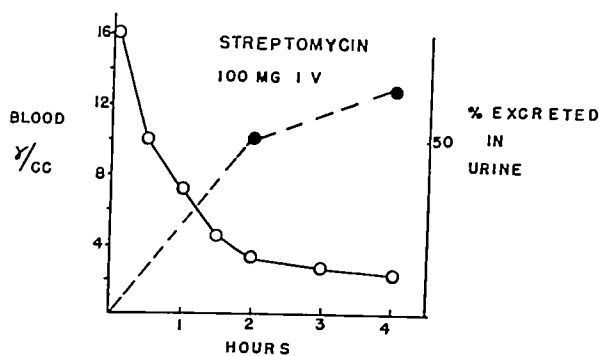


FIGURE 7 Blood Levels (Solid Curve) and Cumulative Urinary Excretion (Broken Curve) of Streptomycin after Single Intravenous Administration (Adapted from Data of Adcock and Hettig²⁸⁵)

attempts to slow the renal excretion of penicillin. The renal plasma clearance is found to be between 755 and 1120 cc per minute,²⁷⁵ and by another investigator²⁸⁸ about 560 cc per minute, figures that approximate the total blood flow through the kidney. These values are to be compared with 12 to 34 cc per minute for sulfadiazine and 4 cc for sulfamerazine.²⁸⁹ Thus, about 80 per cent of penicillin excretion is via the tubules, a fact that early suggested that other tubule-excreted compounds might act as blocking agents. Benzoate (excreted as hippuric acid), p-amino-hippuric acid and diodrast have all been shown to diminish the clearance of penicillin and thereby to raise the average plasma level.²⁹⁰⁻²⁹¹ Water and salt restriction enhance this effect,²⁹² presumably by diminishing the effective renal blood flow, combinations of these methods have succeeded, somewhat irregularly, in increasing plasma levels as much as fourfold to eightfold. However, fluid restriction seems undesir-

able in febrile infections, and some of the compounds employed are not wholly innocuous.

A more subtle method made its appearance with the discovery by Beyer and his associates²⁹³ that a sulfone compound, 4'-carboxyphenylmethanesulfonanilide (caronamide), blocked the tubular excretion of penicillin, reducing plasma clearance to the glomerular rate. The substance interferes with the tubular transport mechanism but does not affect the clearance of a variety of compounds excreted by glomerular filtration.²⁹⁴ Caronamide itself, although it acts specifically upon the tubules, is excreted solely by the glomeruli.²⁹⁵ Clinical experience has shown that ingestion of 2 to 4 gm every three hours is well tolerated by most patients. No case of severe toxicity has been reported,²⁹⁶ although gastric intolerance occurs not infrequently.²⁹¹ The average penicillin plasma level is raised twofold to sevenfold, the duration of detectable levels after a single intramuscular dose of penicillin is appreciably extended, and in general the response to 60 mg (100,000 units) of penicillin approximates that usually seen to 180 mg.²⁹¹⁻²⁹² In aged persons the normal clearance of penicillin is below the average, and caronamide is effective in smaller doses than in younger subjects.²⁹⁷

The great concern about rapid loss of penicillin in the urine originated in the days when the drug was scarce and dosage had to be minimal. The tendency in many clinics today is toward use of very much larger routine doses than had been originally recommended. Should the new repository preparations fulfill their present promise it is quite possible that adequate control of most infections will be achieved by proper choice of the interval at which large doses of such preparations are injected. The use of adjuvant medication of the caronamide type would then be rendered unnecessary.

Streptomycin

From the pharmacodynamic standpoint the properties of streptomycin lie midway between those of the sulfonamides and penicillin. It is practically unabsorbed by the oral route but is not destroyed in the gastrointestinal tract,²⁹⁸⁻²⁹⁹ the convenient route for systemic therapy is thus barred, but employment against enteric pathogens is made possible.³⁰⁰⁻³⁰¹ When the drug is administered intramuscularly the plasma-level curve falls more slowly than that of penicillin, the slow fall being related to the low renal clearance of 30 to 80 cc per minute.²⁹⁹⁻³⁰²⁻³⁰³⁻³⁰⁵ The declining slope of the plasma-level curve indicates a permissible interval of four to six hours between doses. Figure 7 shows the disappearance of streptomycin from the plasma and its appearance in the urine after intravenous administration. An interesting mathematical treatment enabling one to predict plasma-level and time relations with remarkable accuracy, not only for streptomycin but also for other drugs, has been

formulated by Boxer and his co-workers³⁰⁶ With streptomycin the wide variation in thresholds of different organisms, and the real importance of maintaining effective levels to combat the threat of drug fastness should dictate a flexibility of dosage and interval based upon expected levels and checked frequently in each patient

The various methods of topical administration for high local concentrations are just as applicable here as with penicillin. In addition very large doses may be given by mouth in the treatment of intestinal disease caused by gram-negative bacteria or for preoperative sterilization of the bowel

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

CASE 35041

PRESENTATION OF CASE

A forty-six-year-old masseur was admitted to the hospital complaining of intermittent fever

Four months before admission he developed bronchopneumonia and was ill for about three weeks, with a temperature up to 102°F, moderate cough without bloody sputum and slight diarrhea. He received sulfadiazine for one week without benefit and then penicillin. While he was on the latter therapy the course slowly improved. He became asymptomatic during the next few weeks but was unable to regain the 25 pounds he had lost during the acute illness. There was a marked change in his muscular appearance, with definite atrophy, particularly of the muscles of the arms and shoulders. Two and a half months before admission he noted listlessness, easy fatigability and an afternoon temperature to 100.5°F, followed by profuse sweating. There were no night sweats, cough or pain. Febrile rises occurred periodically.

He had had nocturia (twice a night) for many years. The patient's wife stated that he had frequent nausea, vomiting and chest pain. For about five years he had been troubled by migratory ar-

thralgias. On several occasions he had periarticular swelling of the hands and knees, suggesting urticaria. The arthralgias were readily relieved by aspirin, and medical aid was not sought.

Physical examination was negative except for slight pallor.

The temperature was 99°F, the pulse 100, and the respirations 20. The blood pressure was 132/82, systolic, 82 diastolic.

Examination of the blood disclosed a white-cell count of 8600, with 73 per cent neutrophils, 22 per cent lymphocytes, 1 per cent mononuclears and 4 per cent eosinophils. The hemoglobin was 11.8 gm. The specific gravity of the urine ranged between 1.002 and 1.006, with a +++ or ++++ test for albumin. On microscopical examination occasional red and white cells and granular, cellular and hyaline casts were found in the sediment.

The sedimentation rate was 13 mm in one hour. The nonprotein nitrogen was 18 mg, the calcium 8.8 mg and the phosphorus 3.3 mg per 100 cc. The alkaline phosphatase was 3.7 units. A cephalin flocculation test was + in twenty-four and ++ in forty-eight hours. The total protein was 6.95 gm, with an albumin-globulin ratio of 1:1.8. Blood cultures were negative. The brucellergen skin test was negative. Tuberculin (O.T.) was positive in dilution of 1:100 in twenty-four hours, with a 3-cm to 4-cm area of erythema and induration and some pruritus. An electrocardiogram was normal. The basal metabolic rate was +10 per cent.

An x-ray film of the chest was normal. A film of the left knee showed slight hypertrophic changes about the articular surfaces consistent with a slight degree of osteoarthritis. On Graham test the gall bladder filled with well concentrated dye and contained a rounded, nonopaque shadow consistent with calculus. A gastrointestinal series demonstrated a constant narrowing in the prepyloric region for a distance of 3 cm. In the center of the narrowed portion a constant collection of barium,

measuring 1 cm in diameter, was seen. A plain film of the abdomen demonstrated that the right renal shadow was larger than the left.

The hospital course was essentially afebrile, and the patient was discharged seven days after admission. A short time later he was admitted to another hospital, where x-ray studies failed to demonstrate the prepyloric lesion previously found. An intravenous pyelogram and gastric analysis were negative. A gastrointestinal series one month later suggested a duodenal ulcer, with spasm of the antrum. Following discharge the course at home consisted of rather persistent fever and fleeting severe joint pains. There were no objective joint changes, however. Weight loss was progressive. Bloody diarrhea, persistent vomiting and oliguria appeared. He did not become comatose. Joint pains and fever continued up to the end. He died about one month after leaving the hospital.

DIFFERENTIAL DIAGNOSIS

DR WILLIAM W. BECKMAN: The tuberculin test was positive in dilution of 1:100. I assume that it was negative in higher dilutions.

DR TRACY B. MALLORY: I do not believe we know.

DR BECKMAN: Obviously I do not know what this man had. If one reads the present illness, the past history and the routine laboratory work and sets them apart from the rest of the record, one has a history of five years' nocturia (twice a night), and a few months of anemia, albuminuria and pallor, symptoms that seem to have been precipitated by acute infection, and one forms the first impression that this patient was suffering from exacerbation of underlying nephritis, precipitated by acute infection. When one goes on a little further to try to distinguish the nature of the renal disease (I am sure that he must have had some kind of renal disease), it becomes less clear what kind it was. He obviously had some diffuse constitutional disease that gave rise to fever, weight loss, general malaise and so forth. That could be part of the nephritis, although fever is an unusual symptom in that disease. He also seemed to have had some kind of skeletal disease. The changes in his muscular system did not prove as striking on physical examination as one would have expected on reading the history. At any rate, he had some kind of disease that gave him joint pains off and on in the past and ultimately during the final illness were an important feature. Apparently in this hospital no one saw objective signs of joint disease, at least, there is no record. I do not see how one can make a definite diagnosis of the type of joint disease. I suppose we can say that it was consistent with rheumatoid arthritis, but that means nothing. Perhaps the x-ray films will help us decide what the osteoarthritis is. We do not know what symptoms led to the taking of the gastrointestinal series, but

there was some abnormality. Of course, he did have diarrhea and later bloody diarrhea.

DR STANLEY M. WYMAN: I did not plan to show this film. It is not a very impressive picture of arthritis.

DR BECKMAN: It certainly is not—probably normal knees.

DR WYMAN: The films of the chest show questionable diminution in size of the right middle lobe and some increased linear markings, consistent with an old, chronic process with fibrosis. The lung fields are otherwise clear. The heart shadow is not remarkable for a patient of this age. The findings in the gastrointestinal tract as recorded by these films consist of an area of narrowing in the prepyloric and distal antral region, it is seen on all the films. This area on a second examination appears to contain a crater measuring perhaps 1 cm in diameter. The gall bladder shows a small, round, radiolucent shadow consistently on four separate films. The spleen may possibly be a little larger than usual. The right kidney is of normal contour. The left kidney is partially obscured by barium but appears smaller than normal, much like a shrunken kidney. I can see no unusual areas of calcification, no unusual masses and no evidence of destruction of bone.

DR BECKMAN: I suppose at least we can make the diagnosis of a gallstone, but that hardly seems to explain the situation.

This patient had three distinct systems—renal, circulatory and gastrointestinal—involved in this disease, and I suppose the object of this discussion is to try to think of ways in which one can explain most of the symptoms—not all of them—by one diagnosis. I do not know that I can. When one reads the history of the present illness, one thinks of chronic nephritis, but the lack of any nitrogen retention is very much against that. Chronic pyelonephritis or chronic glomerulonephritis would not cause as many symptoms as this did. So I do not believe that either of those diagnoses need be entertained too seriously. I do not know how one can absolutely rule them out, although I would expect nitrogen retention if the patient was as sick as this from chronic pyelonephritis or chronic glomerulonephritis. One has to give consideration to the fact that at the onset of the illness he had received sulfonamides, which are known to cause a type of renal lesion. Dr Mallory has taught us to believe lower-nephron nephrosis is reversible so one would anticipate that the patient would either have died sooner or have been better by this time.

I was interested in the x-ray film of the knees because I thought if the patient had rheumatoid arthritis, one would have to entertain the possibility of amyloid disease, which is frequently a complication of rheumatoid arthritis and in which some people say, at any rate, albuminuria and other evidence of renal disease can occur without much

nitrogen retention and without high blood pressure. This man did not have high blood pressure in the one recording we have. I have no way of ruling out amyloid disease. It would explain a number of the symptoms and possibly the fact that the spleen was in the upper limits of normal by x-ray study, even if not palpable. There is no way to establish that diagnosis, however, it is just something one mentions tentatively.

Of course there is always periarteritis nodosa to be thought of with this sort of symptomatology. It produces gastrointestinal symptoms, skeletal symptoms and renal disease. It has many different kinds of manifestations, and I do not see how one can make the diagnosis clinically, unless there is asthma or a high eosinophil count in conjunction with these symptoms. In 1939, when Dr Short was making out the diagnostic file for the Arthritis Clinic, a great many routine records were reviewed and it was decided that an eosinophil count of 4 per cent was the upper limit of normal. The pulmonary disease in this case was acute infection, not asthma. Perhaps some of the findings seen in the x-ray film are the result of periarteritis nodosa, I do not know. There is no way of establishing it or ruling it out, but it would explain all the symptoms.

Someone obviously thought of undulant fever as a possibility. One of my students just told me that he thought that that was the diagnosis in this case because all the symptoms that this patient had have been ascribed to undulant fever. Considering how often the brucellergen skin test is non-specifically positive, I would be unwilling to make the diagnosis in the face of a negative test. I doubt if all the things ascribed to undulant fever are due to it.

The most likely bet that I can make is that the patient had periarteritis nodosa. I am puzzled by the terminal bloody diarrhea, which suggests ulcerative colitis more than anything else, and also because of the fact that he had diarrhea at the onset of the illness. That is not usually a feature of periarteritis. I am at a loss to explain that. It is possible that he had ulcerative colitis as a terminal event, it sometimes happens. As I have said, beyond making the diagnosis of gallstones that show up by x-ray study, I have to speculate about the rest. Certainly he had a generalized constitutional disease that involved the kidneys, joints and gastrointestinal tract, and periarteritis nodosa would explain it.

DR WALTER S. BURRAGE: There are one or two points of interest not clearly brought out in the history. The patient had severe joint symptoms early in the game. He went to his place of occupation from his home on quite a number of occasions when he had to have crutches and be assisted in and out of the bus by the bus driver. The joint symptoms in the feet, ankles and knees were, there-

fore, more than of fleeting discomfort at such times.

One other point: the joint symptoms came earlier than the so-called pneumonia—that is, before he had been given sulfonamides.

In regard to Dr Beckman's question about the reason for taking the gastrointestinal series—it was ordered primarily because the patient had considerable nausea and vomiting, but also because we were trying to think of every possible lead. To our great surprise we found a local lesion. There was very little in the history to suggest this. When I saw him originally the possibility of some allergic manifestation was considered, such as angioneurotic edema. It soon seemed obvious, however, that an allergic mechanism was unlikely but that if present at all, it must have been of the delayed reaction type, which one thinks of in connection with periarteritis nodosa. There was little evidence for chronic arthritis. Periarteritis nodosa seemed the most likely diagnosis but one made with only modified enthusiasm.

DR JOHN W. CASS: During the past four or five years I saw him once in a while when his family physician was away. He asked me first to see him because he was acutely ill and had a temperature of 104°F. He complained bitterly of pain in the joints, although it was not possible to see anything abnormal about the joints. He could not move them without excruciating pain. This quieted down. He said it was like all the attacks except that there was no swelling. I asked him to call me if he had swelling again. Two years later he called and said that he had another attack with swelling. He had definite swelling of the hands, but more like urticaria than joint swelling. I did not see him again until he became very ill. I thought the patient had some type of atypical rheumatoid arthritis, and I referred him to Dr Burrage because the one time that I had seen him in an attack of joint pain and swelling I thought that it resembled angioneurotic edema. The urine was examined several times, and it was apparent from that time on that he had progressive signs of kidney disease. The albuminuria increased, there were more casts, and the amount of urine was definitely less. The terminal picture was one of wasting disease with definite signs of kidney disease. He definitely had atrophy of the muscles. There was no question about it. It may have been atrophy of disuse, but at the same time it was far out of proportion to what one would expect. I saw him within an hour of his death and did not realize that he was going to die so soon. I expected him to die in clear-cut uremia, but he was not drowsy. The only thing that I was clear about was that he had a terminal stage of some generalized disease. At first the picture seemed like rheumatoid arthritis, terminally, it was more in keeping with periarteritis nodosa.

CLINICAL DIAGNOSES

Fever of unknown etiology
 Periarteritis nodosa

DR BECKMAN'S DIAGNOSES

Periarteritis nodosa
 Gallstone

ANATOMICAL DIAGNOSES

Diffuse myeloma of the bone marrow
Amyloidosis of liver, spleen and kidneys
Superimposed Bence-Jones proteinuria, kidney?
 Gastric ulcer, healed
 Cholelithiasis
 Hemorrhagic enteritis
 Arteriosclerosis, generalized, moderate

PATHOLOGICAL DISCUSSION

DR MALLORY The autopsy on this man showed an enlarged liver and spleen and very greatly enlarged kidneys. The liver was very pale and firm and slightly waxy in character. The spleen presented visible granulations in the region of the corpuscles. The gross appearance was so characteristic of amyloid disease that an iodine reaction was done at the time of autopsy and was strongly positive. The gastric lesion appeared to be an old, partially healed, benign, peptic ulcer very close to the pylorus. At the time of autopsy we found nothing that would explain the existence of amyloidosis in this patient.

When the microscopical sections came through it was obvious that the majority of the bone marrow was replaced by immature cells only faintly resembling plasma cells but, nevertheless, within the limits of what we see in certain cases of multiple myeloma. Sometimes very severe amyloidosis does occur in association with myeloma, and I believe that is the histologic background in this case. The kidneys were very remarkable in that they showed only mild amyloid deposits but the most severe hyaline degeneration in the convoluted tubules that I have ever seen. There were also very numerous casts in some of the lower tubules. I did not pay much attention to them at first, but one of the pathologists, not knowing the history of the case, asked me if the man had a myeloma so there may also have been a Bence-Jones element in these kidneys as well as amyloidosis. The urine was never examined for Bence-Jones protein so that we are unable to determine that

CASE 35042

PRESENTATION OF CASE

A seventy-four-year-old egg tester was admitted to the hospital because of vomiting of four days' duration.

He had been well and working up until about three months before entry, when he suddenly

developed nausea, vomiting and generalized cramping pain. He also noted diarrhea, the stools being brown, liquid and not bloody. He was admitted to another hospital, where physical examination revealed a semicomatose man in acute abdominal pain. The skin was cold and clammy. The abdomen was slightly distended, tender and tympanic, and no peristaltic sounds were heard. The prostate was slightly enlarged. The blood pressure was 158 systolic, 70 diastolic. The temperature was 100°F (rectally). The urine had a specific gravity of 1.012 and gave a ++ test for albumin, and the sediment contained 0-2 white cells and 2-4 red cells per high-power field and + bacteria. The red-cell count was 3,970,000, with a hemoglobin of 11.7 gm, and the white-cell count 7750, with 63 per cent neutrophils. The blood sugar was 135 mg per 100 cc, the nonprotein nitrogen 136 mg per 100 cc, the carbon dioxide 32.5 milliequiv per liter and the amylase 64 units. A guaiac test of the stool was +++. A roentgenogram showed gas in the stomach and left colon. The kidneys were well outlined and normal in size, shape and position. The cecum and transverse and ascending colon were distended by gas, and barium flowed freely through the splenic flexure. The patient was unco-operative, and the examination was unsatisfactory. Three days later an upper gastrointestinal series revealed no abnormality in the esophagus, stomach or small bowel. A six-hour film showed the terminal ileum, cecum, transverse colon, descending colon and sigmoid partially outlined by barium. He was placed on Miller-Abbott tube for distention and given intravenous fluids, streptomycin and penicillin. Agglutination tests for typhoid O and H antigens, paratyphoid A and B and Proteus OX-19 were reported as negative. Stool culture showed no enteric pathogens. Repeated blood cultures were negative. After three days of therapy the nonprotein nitrogen was 162 mg, total protein 4.7 gm per 100 cc, phosphorus 5.5 mg per 100 cc and uric acid 11.8 mg per 100 cc. The diarrhea continued unabated. Intravenous fluids were continued but stopped on the twentieth hospital day. The temperature had fluctuated throughout the hospital stay between 99 and 101°F, rectally. The diarrhea began to come under control, and fluids were given more and more by mouth. The stool guaiac tests became negative, and on the eighteenth hospital day the nonprotein nitrogen had fallen to 32 mg per 100 cc and the carbon dioxide combining power had risen to 43 vol per cent. The urine specific gravity throughout the hospital stay remained fixed between 1.007 and 1.013. There had been continuous microscopical pyuria, the sediment averaging 15 to 25 white blood cells per high-power field. He remained very weak, and in view of what was considered to be the chronic nature of his disease, it was recommended that further care be continued in a chronic-disease hospital. He was

discharged to a convalescent home, where he remained two weeks

In the interval, some seven weeks before admission to this hospital, the patient felt well with no specific complaints. Four days before entry he became confused and incontinent of urine. On the following day he began vomiting, became increasingly weak, and for forty-eight hours before admission had been unable to retain anything by mouth. The vomitus was occasionally "green bile" and never contained blood or coffee-grounds material. The bowels had moved regularly. There was some right abdominal and left chest pain.

Twenty-five years previously he was operated on for a "twisted bowel," which was "untwisted at the time of operation." For six years prior to admission he had noted episodes of diarrhea occurring every three or four months. For five years before admission he experienced urinary incontinence and nocturia. His normal weight had been 210 pounds, and a daughter stated that he had been losing weight progressively.

Physical examination revealed a somewhat disoriented, pale, dehydrated, elderly man in no acute distress. He regurgitated a green fluid regularly. The chest was clear, the diaphragm was high. There were dullness and decreased breath sounds and vocal fremitus at the right base, with egophony above. The heart was not enlarged to percussion. The abdomen was mildly distended and tympanitic throughout. Peristalsis was decreased but of normal pitch. There was some tenderness on the left but no rebound tenderness. There were no rectal masses. The prostate was somewhat enlarged. The legs and sacrum showed a + edema.

The temperature was 98.6°F, the pulse 94, and the respirations 24. The blood pressure was 90 systolic, 60 diastolic.

The urine had a specific gravity of 1.012 and gave a + test for albumin, and the sediment contained 4-5 white blood cells and a rare red blood cell and hyaline cast per high-power field. The red-cell count was 3,500,000, with a hemoglobin of 13 gm, and the white-cell count was 15,100, with 94 per cent neutrophils. The blood nonprotein nitrogen was 48 mg and the total protein 4.8 gm per 100 cc, the chloride 102 milliequiv and the sodium 143.9 milliequiv per liter, and the blood sugar 104 mg per 100 cc. A stool gave a + guaiac reaction. On the following day the nonprotein nitrogen was

56 mg and the total protein 4.5 gm per 100 cc, the chloride 94 milliequiv, the carbon dioxide 28.1 milliequiv, the sodium 141.7 and the potassium 3.8 milliequiv per liter. A culture of the bladder washings grew abundant gram-negative cocci and colon bacilli.

In the hospital the patient was kept on intestinal suction and intravenous fluids. He became oliguric, the urine output being 100 cc in the first twenty-four hours after admission. He remained disoriented. A roentgenogram of the abdomen on the day of admission showed the Harris tube in the stomach. The colon was filled with gas and fecal material but was not definitely dilated. Gas and fecal material were present in the rectum. There were dilated, air-filled loops of small bowel. A roentgenogram of the chest showed homogeneous ground-glass density on the right and patches of increased density on the left. On the second hospital day the white-cell count rose to 25,000, with 98 per cent neutrophils. The urine contained many white blood cells. The temperature was 99°F. On the third hospital day his outward appearance was about the same. He was still confused. The abdomen appeared to be a little more distended. Peristalsis was absent. There were more resistance and tenderness in the lower quadrants. The temperature rose as high as 100°F, and the pulse and respirations remained at 120 and 24, respectively. The urine output was negligible. The white-cell count was 22,500, with 98 per cent neutrophils. Twenty-four hours later the temperature was 99.4°F, the pulse 115, and the respirations as high as 28. The blood pressure was 70 systolic, 40 diastolic. The urine output during the previous day had been less than 50 cc. The nonprotein nitrogen was 90 mg per 100 cc, and the chloride 93 and the carbon dioxide 25 milliequiv per liter. On the following day the patient was semicomatose, with a uremic odor. On the following morning he died.

DIFFERENTIAL DIAGNOSIS

DR DANIEL S. ELLIS: It seems to me that the object of this case is primarily to state whether or not this patient had some intra-abdominal disease in addition to renal disease, which is quite apparent. At the time of the first admission because of abdominal pain, nausea and vomiting he was found to have definite evidence of renal disease and uremia, and in the subsequent course of events he was treated with antibiotics and paren-

teral fluids The gastrointestinal symptoms disappeared, the urinary function returned to approximately normal and he was discharged It is unfortunate that this admission was at another hospital because we do not have the x-ray films Therefore, we have to take at face value the statement that no gastrointestinal-tract disease was demonstrated by the various barium examinations done at the time of this illness

There are several things that make me wonder a little as far as the abdominal pain, nausea and vomiting and diarrhea are concerned In the absence of any demonstrated abnormal signs, either on physical examination or x-ray examination of gastrointestinal tract or abdomen, I am forced to believe that the gastrointestinal symptoms were on the basis of uremia It is well known that patients with uremia may have abdominal pain, diarrhea and an ulcerative process involving the entire gastrointestinal tract The only thing that makes me hesitate a little bit is the amylase report of 64 units This is high in our laboratory This is only one report, and I think that I will merely mention it as being abnormal This man could have had pancreatitis The low white-cell count is a little bit against it The fact that examination later showed a leukocytosis makes me think that if he had had a real pancreatitis or intra-abdominal infection at the time of the first admission, it would have been evidenced by an elevation of the white-cell count, which was not observed I believe that he was uremic, that he was moderately acidotic, and that he was having diarrhea and bloody stools on the basis of renal disease This theory is further supported by the fact that when treated with supportive measures tending to rehydration to stimulation of urinary output and to control of infection, he improved, and his abdominal symptoms subsided At the time of discharge he was not having diarrhea, pain, nausea or vomiting, the nonprotein nitrogen was normal but he still had white cells in the urine

The second episode of illness, as much as I have studied it and tried to arrive at a decision, I am unable to make anything more of than an exacerbation of renal disease in an elderly man, with renewed renal failure and uremia This time he did not have as much diarrhea He did have a markedly increased leukocytosis and at this time had a positive urine culture I would like, if

possible, Dr Wyman, to see any films that you may have to be sure again that some trouble in the abdomen was not developing and to make sure that he did not have pneumonia

DR STANLEY M WYMAN These portable films taken on a very sick patient are of poor quality They show hazy, homogeneous density in the right chest laterally, which obscures the right leaf of the diaphragm and appears quite consistent with fluid The right lung shows, as far as I can see, no definite intrinsic disease, and I am unable to see any active process going on in the left lung The film of the abdomen shows, as reported, gas in nondilated loops of large and small bowel down to the rectum I do not see any unusual masses or any abnormal calcification except in the prostate

DR ELLIS Would you say there was any difference between the distention in the large or the small bowel? Is there any point of obstruction that you can see?

DR WYMAN No, I cannot make a diagnosis of either large-bowel or small-bowel obstruction

DR ELLIS This patient is said to have been operated on once for volvulus of the intestinal tract. It is reported that this was untwisted at the time. At the present admission he had nausea and vomiting, the vomitus containing bile, so that he was regurgitating small-bowel contents Certainly I could not exclude the possibility that he had an intestinal obstruction On the other hand, I do not believe this to be true I believe that the distention seen in the x-ray film is that of a critically ill, elderly man, and the gas-filled loops are probably those of ileus and loss of tone rather than obstruction The vomiting also I think, goes with the renal disease I am going to say that all the symptoms are on the basis of renal disease

The problem is, What kind of renal disease or urinary-tract disease did this man have? I cannot get away from the definite evidence of an infection, which was manifested by the large number of white cells, positive urine culture and a white-cell count going as high as 22,500 So I believe that we are probably dealing with chronic pyelonephritis rather than a chronic glomerulonephritis The fall in blood pressure throughout the illness, I think, was probably not due to any acute coronary insufficiency but to a debilitating illness, gradually progressing, in an acutely toxic, critically ill man, who probably had some pneumonia and atelectasis, but I do not

believe we can say that he had lobar pneumonia. The fluid in the chest and the pitting edema can be explained by a combination of things—for example, the low serum protein, uremia and renal disease.

My final diagnosis, without “hemming and hawing” any more, is that the patient had chronic pyelonephritis with uremia. He had some terminal atelectasis or bronchopneumonia and a right hydrothorax, and I have insufficient evidence to go any farther. I do not believe that he had any intra-abdominal disease. As already mentioned from the record there is a possibility of pancreatitis and possibly he had had volvulus of the small bowel with obstruction to account for the nausea and vomiting, but I would question that. I cannot make a diagnosis of intra-abdominal disease on the history as given.

DR DONALD S. KING: I had an advantage over Dr. Ellis because I saw this patient while he was alive and I had a chance to examine his abdomen. In fact, the day before he died I sat down with his problem and put my conclusion in the record. However, I did not do well. We were confused at first because he seemed to be having exactly the same symptoms when we saw him as he had had in the other hospital. He was discharged from that hospital with a diagnosis of uremic gastroenteritis, and he seemed to get along perfectly well on that diagnosis until he was admitted to our wards. Our first impression was that he again had uremia with gastroenteritis, and this diagnosis was sustained in part by the oliguria. But when we found that his nonprotein nitrogen was around 50 mg per 100 cc, we began to doubt whether uremia would explain all the findings. We were particularly disturbed when his white-cell count began to rise. But I never realized how serious his abdominal condition was, and I thought that he might have a mesenteric thrombosis.

DR ELLIS: There is no detailed report of the examination of the abdomen, which might be fairly important. It just says that there was resistance and tenderness in the lower quadrant. Did he have real spasm and tenderness? If so, was it in the region of the bladder and the lower ureter?

DR KING: There was no marked tenderness or spasm that I can recall. Is Dr. Littlefield here? He knows more about that.

DR JOHN W. LITTLEFIELD: I agree to that. The initial surgical examination will describe it, I think.

DR KING: The record states that on examination the patient was pale, slightly disoriented and acutely ill. The abdomen was full and soft, and then the record says “tender”—but does not state where—without masses and with absent peristalsis. At that time the surgeon thought that uremia would be a satisfactory diagnosis.

DR ELLIS: Was the patient ever sigmoidoscoped?

DR KING: I think he was not. He was a very sick man.

DR ELLIS: It is obvious that he had an ulcerative process going on in the intestinal tract. I think that there are any number of possibilities if he did not have what I have previously said. I think he had. But on the basis of the record I have to leave it there.

DR TRACY B. MALLORY: I would like to ask if the clinicians remember any patient with uremic enteritis who recovered from the episode.

DR MARIAN ROPES: I cannot remember having seen it.

DR MALLORY: It is a fairly common condition immediately before death, and I do not know whether the patient ever recovers from it or not.

DR KING: The discharge diagnoses from the other hospital were chronic nephritis, uremia, uremic gastroenteritis and benign prostatic hypertrophy.

DR ELLIS: I should like to ask Dr. Ropes if the uric acid of 11.8 mg per 100 cc is of any significance.

DR ROPES: At the time he had evidence of so much retention that I think it means nothing.

CLINICAL DIAGNOSES

Chronic nephritis, with uremia
Intestinal obstruction of undetermined cause.

DR ELLIS'S DIAGNOSES

Chronic pyelonephritis
Chronic glomerulonephritis?
Uremia
Right hydrothorax
Bronchial pneumonia — atelectasis
Generalized arteriosclerosis
Benign prostatic hypertrophy

ANATOMICAL DIAGNOSES

*Carcinoma of colon, with probable perforation**Generalized peritonitis**Nephrosclerosis*

Cholecystitis and cholelithiasis

Anasarca

Benign prostatic hypertrophy

Operative wound, old posterior gastroenterostomy

PATHOLOGICAL DISCUSSION

DR MALLORY The autopsy on this patient, I am sure, was a complete surprise to everyone. The major lesion was a cancer of the bowel located at the splenic flexure. This was about 4 cm long, completely encircling the bowel, which was very deeply ulcerated. There was a generalized fibrinopurulent peritonitis of sufficient age so that it had become separated into a great many pus-filled cavities, separated from one another by fibrinous adhesions. Actual perforation of the bowel could not be demonstrated with a probe at the time of autopsy, but since one of the larger intra-abdominal abscesses was in the immediate neighborhood of the lesion, I have no doubt that it had perforated and was the source of the peritonitis.

The lungs showed very marked congestion, atelectasis and edema but no pneumonia. There was pleural effusion of 900 cc on the right side. The kidneys weighed just over 300 gm, had a slightly narrowed cortex and microscopically showed a severe degree of arteriolar narrowing and hyalinization—the type of kidney one would expect to see with a benign hypertension. The process did not look far enough advanced to have in itself been the cause of the uremia, although to try and guess

from the appearance of such a kidney whether or not the patient had uremia is very dangerous, of course.

The former operation, described only as an operation for twisted bowel, had been a gastroenterostomy. We found nothing to explain why that had been done. The gastroenterostomy was patent. Our opinion was that the patient had a moderate grade of vascular nephritis, which probably alone would not have produced uremia but did so in association with peritonitis, and the dehydration that would go with that. A considerable degree of nitrogen retention is a common phenomenon in general peritonitis.

DR ELLIS Did he have the peritonitis when he was admitted to the first hospital?

DR MALLORY I cannot say whether or not he had some degree of peritonitis in the upper abdomen the first time. He had some old, fibrous adhesions, which were most extensive in the region of the previous operative scar. I do not believe I can say whether some of them were produced by an attack of localized peritonitis weeks before at the time of the first illness. They may have traced way back to the original disease twenty-five years previously.

DR ELLIS It is quite possible that peritonitis was at first controlled by the streptomycin and penicillin. After these were stopped it flared up again in more chronic, localized form. It certainly is true that we often see kidneys that are borderline and then tipped into failure by any acute process. I think it possible in view of the findings to explain the uremia on that basis. It seems strange that the peritonitis was not more manifest clinically.

DR KING We thought so too.

DR MALLORY The paralytic ileus was the only evidence positively in favor of it.

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BUDGET FOR 1949

As THE country enters into that period of the year immediately following the winter solstice when it wrestles, individually and collectively, with its fiscal problems, some thought must also be given to the pecuniary affairs of the Massachusetts Medical Society. These affairs, as the Treasurer will bear witness, have grown, shortly the Council will vote upon the largest budget in the history of the Society.

None of the items in this budget need cause concern, for the Society is solidly solvent, all of them require the scrutiny of the councilors, who should have a clear conception of the magnitude of the works that they are directing and their importance.

The largest single item in this budget is the \$27,000 that goes to the support of the Boston Medical Library, and represents one of the important reasons for the increase in the Society's membership assessment in 1948. For the five dollars of his assessment that is so allocated, each fellow of the Society receives membership in the Library and, perhaps more important, the consciousness that he is contributing a modest share toward the support of a basic factor in medical education and in intellectual improvement in his profession. This support must be reaffirmed so long as it is needed, as one of the soberest and most mature commitments that a physician can make.

Other items in the Society's budget are concrete evidence of the fact that the relation of physicians to the public have changed, that they have become more complex and that they are subject to pressures that call for constant strengthening from within. The payroll has justifiably increased as headquarters duties have become more numerous and more exacting. The expenses of the officers and committees in discharging their functions have increased, a considerable share of this increase being charged to public relations, including the expenses of the Committee on Legislation, the refund to the district societies was increased last year from \$4000 to \$8000, the employees' pension plan adds \$4000 yearly, the Council has voted \$10,000 annually to the Medical Benevolent Society.

The sum of \$10,000 has again been allocated to the *Journal* as the only commitment that the Society is presently asked to make for over 6000 subscriptions and the publication of the Proceedings, in four years \$5000 only of this appropriation has been retained for the use of the *Journal*.

The budget requested for 1949 is \$142,155, the income of the Society being probably over \$150,000. The margin is safe, but it must in the future as at present be carefully guarded.

SWORDS AND PLOUGHSHARES

How can health and medical-care standards of American soldiers and airmen be kept at their present level, the highest of any army in the world today? The Army Advisory Committee* asks the

*To save — not to destroy. Bull. Army Advisory Committee 2 1, October 1948.

question, one answer to which may be found in the Medical Department's plan for peace-time operation of Reserve Officers Training Corps units in the approved medical schools of the United States. An account of the work of these units within the framework of the undergraduate medical curriculum is given elsewhere in this issue of the *Journal*. To those whose recollections of medical ROTC are strongly colored by past experience of litter bearing and close-order drill, unmistakable signs of progress will be revealed.

ROTC units now installed are designed to obtain a total enrollment of 8000 for all four classes in medical schools, and to produce annually about 2000 first lieutenants. In the year 1946-1947, 20 units were in operation, in 1947-1948, 23 units were added, and in 1948-1949 there are an additional 6, bringing to 49 the total units now operating. Within a period of three years this has therefore become a universal feature of medical education in the United States. On a similar elective basis the Army has established 18 units in the dental schools, 6 in the veterinary schools, and 4 in the schools of pharmacy.

The purpose of the medical ROTC is to develop a body of Reserve Medical Corps officers who will be capable of performing professional duties and also of taking care of themselves within the structure of the Army, and without further training on mobilization day—or at any time when they may be called to active service. A secondary mission of the plan is that of acquainting the medical student with the facts concerning a career in the Army Medical Department, with the further possibility that he will become interested in obtaining an Army internship and in applying for a regular commission.

All this is preparedness in the best sense—preparedness to save—not to destroy, to conserve—not to dissipate. It is preventive medicine, organized on a scale and basis heretofore unknown.

A MEETING OF MINDS

PHYSICIANS are making up their minds about the future of the broad field of psychiatry, as evidenced by the International Congress on Mental Health, held in London in August, 1948. Two thousand men and women, representing fifty-five

countries, at that time discussed mental health and formulated specific plans for its betterment throughout the world. Although the largest number of participants were psychiatrists, the preliminary study groups were made up not only of physicians but also of psychologists, sociologists, anthropologists, educators, theologians and representatives of relevant disciplines.

The purpose of the Congress was threefold: to bring together psychiatrists from all the world, that they might secure an over-all picture of the psychiatric needs of human beings and formulate methods of solving these problems, to study the psychologic causes of war and the part physicians may play in prevention, and to form an international organization to engage actively in promoting mental health in every nation.

Representatives from fifty-five countries participated in the incorporation of this organization, with offices in Geneva. Membership is made up of professional societies in the related disciplines concerned with mental health as well as of the mental-hygiene societies in each participating country. These member associations will send representatives to the annual meeting of the Mental Health Assembly. It is expected that the work of the World Federation for Mental Health will be incorporated with the World Health Organization and the whole correlated with the United Nations Organization, the World Federation offering a means for transnational collaboration on the problems of mental health.

There can be no question that this is a most important development in the field of medicine and one in which physicians will be interested and in which they will want to participate, for mental illness is probably the greatest single cause of suffering throughout the world, and it is to physicians that people must turn for individual treatment, guidance and public-health measures directed toward its prevention. For the first time in history these facts are now generally recognized, and the organization that has been perfected deserves support. To this end physicians are increasing their knowledge of the physiologic, psychologic and sociologic factors relating to mental health, that they may be better prepared to treat patients, formulate mental-

hygiene principles and implement measures for the improvement of mental health

Plans have been completed for the President of the United States to proclaim a Mental Health Week in April, 1949. This will be followed by proclamations from the governors of the forty-eight states and wide publicity through press and radio. There will be active co-operation from medical societies and other organizations directed toward the betterment of mental-health conditions in this country. In all this the medical profession will assume the leadership that it has always shown in matters pertaining to individual and public health.

PIED PIPERS OF MADISON

CURRENT researches in the department of zoology of the University of Wisconsin on the habits of rodents are beginning to reveal interesting facts concerning the life and manners of these small inhabitants of the underworld. As a result it is believed that a careful study of the life habits and population cycles of rats, bats, mice and muskrats may lead to improved methods of rodent control.

Five College of Agriculture animal buildings, infested with wild mice, comprise the location of the study, here eager scientists, employing the reverse process of belling the cat, are catching and marking the diminutive enemies of the new look.

A number of facts have already been elicited. Mice, when living in peace and comfort, rarely range more than 30 or 40 feet from home, and rats seldom farther than 100 feet from the food supply. Since the rate of reproduction averages 30 young per year per female with about 5 survivors, overpopulation soon becomes a factor, however, with competition and outbreaks of civil war resulting, as with human beings. Perhaps from this analogy the frequently quoted question may arise "Are we men or are we mice?"

Various methods of rodent control have been tested and evaluated. The best of these is prevention, and to discourage the rodent population this implies cutting off the food supply. Entry holes must be plugged, garbage removed, refuges cleaned and cupboards either mouseproofed or kept as bare as

Mother Hubbard's. Rats abandoning their native locality for any reason are never welcomed into another colony.

In the frontal attack poisoning is the least effective weapon, a good hunting cat one of the best. The old-fashioned snap-trap remains a steadily effective mouse-eliminator. Not mentioned as participating in the Wisconsin field trials is a new and remarkable gadget for the mass liquidation of domestic rodents. This machine, equipped with an electric eye, is set up adjacent to a rat runway. When a victim crosses the beam he is quietly seized by the neck, electrocuted and tossed aside, after which this supreme effort of the electrocutioner's art promptly resets itself.

The rodent population so far is nearly holding its own, but to do so it must live dangerously.

Fourth-year students in approved medical schools are reminded of the *Journal's* prize essay competition on preventive medicine. For further information see *The New England Journal of Medicine*, September 30, 1948, p 525, or write to the editor.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

ABBE — Alanson J. Abbe, M.D., formerly of Fall River, died on January 3. He was in his eighty-eighth year.

Dr. Abbe received his degree from Harvard Medical School in 1885. He was formerly secretary-treasurer of Bristol South District Medical Society and ophthalmic surgeon at Union Hospital, Fall River.

A son, a daughter and two grandchildren survive.

CHENERY — William E. Chenery, M.D., of Brookline, died on January 3. He was in his eighty-fifth year.

Dr. Chenery received his degree from Harvard Medical School in 1890. He was formerly surgeon at St. Elizabeth's Hospital, consultant at Boston Dispensary, New England Deaconess and Evangeline Booth hospitals and a member of the staff of New England Baptist Hospital. He was a member of the American Academy of Ophthalmology and Oto-Laryngology, American Laryngological and Rhinological and Otological Society and a fellow of the American College of Surgeons and American Medical Association.

His widow and a niece survive.

GOLDBERG — Samuel B. Goldberg, M.D., of Medford, died on January 5. He was in his forty-sixth year.

Dr. Goldberg received his degree from Middlesex University School of Medicine in 1923.

His widow, a son, a daughter, three brothers and a sister survive.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATH

STICKNEY — Henry L. Stickney, M.D., formerly of Manchester, died on December 17. He was in his seventy-eighth year.

Dr. Stickney received his degree from University of Vermont College of Medicine in 1894. He had served in various Veterans Administration hospitals and at one time owned and operated the Hillcrest Hospital in Manchester. He was formerly a member of the staff of the Mayo Clinic, Rochester, Minnesota, and was a fellow of the American Medical Association.

His widow, two sons, a daughter, a brother, eight grandchildren and a great-grandchild survive.

MASSACHUSETTS DEPARTMENT
OF PUBLIC HEALTHCOMMUNICABLE DISEASES IN
MASSACHUSETTS FOR DECEMBER, 1948

DISEASE	RÉSUMÉ		
	DECEMBER 1948	DECEMBER 1947	SEVEN-YEAR MEDIAN
Chancroid	3	6	3*
Chicken pox	3022	1680	1444
Diphtheria	47	36	29
Dog bite	668	616	517
Dysentery, bacillary	2	19	12
German measles	83	64	68
Gonorrhea	257	262	316
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	1	2	1*
Malaria	0	7	7
Measles	4674	459	702
Meningitis meningococcal	8	2	12
Meningitis Pfeiffer bacillus	5	8	3
Meningitis pneumococcal	7	3	6†
Meningitis staphylococcal	1	0	0†
Meningitis streptococcal	0	0	0†
Meningitis undetermined	6	4	3†
Mumps	1319	1267	1080
Pneumonia, lobar	140	96	208
Polioomyelitis	2	8	11
Salmonellosis	4	9	5
Scarlet fever	699	475	978
Syphilis	180	274	372
Tuberculosis pulmonary	217	210	207
Tuberculosis, other forms	16	14	13
Typhoid fever	2	4	4
Undulant fever	1	4	3
Whooping cough	331	682	682

*Four year median

†Six-year median

COMMENT

Diseases above the seven-year median were chicken pox, diphtheria, German measles and mumps.

Diseases below the seven-year median were bacillary dysentery, lobar pneumonia, poliomyelitis, scarlet fever, typhoid fever, undulant fever and whooping cough.

Diphtheria was still too prevalent. For ten consecutive years, 1936-1946, the incidence was lower than that during December. A total of 139 cases was reported during the last four months of 1948, compared to 85 cases in the same period in 1947.

The incidence of chicken pox was the highest ever reported for December, and that for measles was the highest since 1925. The frequency of mumps, which was still higher than the seven-year median, seems to be declining.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Arlington, 3, Blackstone, 1, Boston, 23, Bridgewater, 1, Brookline, 1, Chelsea, 2, Danvers, 2, Everett, 2, Haverhill, 1, Lowell, 1, Nahant, 4, Revere, 1, Salem, 1, Somerville, 1, Springfield, 1, Waltham, 1, Winchester, 1, total, 47.

Dysentery, amebic, was reported from Boston, 1, total, 1. Dysentery, bacillary, was reported from Boston, 1, Worcester, 1, total, 2.

Encephalitis, infectious, was reported from Andover, 1, Malden, 1, Westfield, 1, Worcester, 1, total, 4.

Lymphocytic choriomeningitis was reported from Winthrop, 1, total, 1.

Meningitis, meningococcal, was reported from Boston, 1, Harwich, 1, New Bedford, 1, Pittsfield, 1, Somerville, 2, Williamstown, 1, Winthrop, 1, total, 8.

Meningitis, Pfeiffer-bacillus, was reported from Malden, 1, Southbridge, 1, Springfield, 3, total, 5.

Meningitis, pneumococcal, was reported from Braintree, 1, Chesterfield, 1, Gloucester, 1, Medford, 1, Somerville, 1, West Springfield, 1, Weston, 1, total, 7.

Meningitis, staphylococcal, was reported from Chicopee, 1, total, 1.

Meningitis, undetermined, was reported from Adams, 1, Avon, 1, East Brookfield, 1, Milton, 1, West Boylston, 1, Worcester, 1, total, 6.

Polioomyelitis was reported from Hardwick, 1, West Springfield, 1, total, 2.

Salmonellosis was reported from Boston, 2, Lynn, 1, Winchester, 1, total, 4.

Septic sore throat was reported from Boston, 4, Medford, 2, total, 6.

Tetanus was reported from Lawrence, 1, total, 1.

Trichinosis was reported from Boston, 1, total, 1.

Tularemia was reported from Sandwich, 1, total, 1.

Typhoid fever was reported from Boston, 1, Swansea, 1, total, 2.

Undulant fever was reported from Grafton, 1, total, 1.

CONSULTATION CLINICS FOR CRIPPLED
CHILDREN IN MASSACHUSETTS

The December schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

CLINIC	DATE	CLINIC CONSULTANT
Haverhill	February 2	William T. Green
Lowell	February 4	Albert H. Brewster
Salem	February 7	Paul W. Hugenberger
Gardner	February 8	Carter R. Rowe
Brockton	February 10	George W. Van Gorder
Worcester	February 11	John W. O'Meara
Greenfield	February 14	Charles L. Sturdevant
Springfield	February 15	Garry deN. Hough, Jr.
Pittsfield	February 16	Frank A. Slowick
Hyannis	February 24	Paul L. Norton
Fall River	February 28	David S. Grace

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

MISCELLANY

PRESIDENT OF THE AMERICAN ACADEMY
OF PEDIATRICS

Dr. Warren R. Sisson, of Boston, having served for a year as president-elect of the American Academy of Pediatrics, has assumed the office of president. Dr. Sisson, a graduate of Johns Hopkins University School of Medicine and formerly a member of the Department of Pediatrics of Harvard Medical School, served also as chairman of the committee for the Study of Child Health Service of the Academy.

CORRESPONDENCE

STATISTICS OF PNEUMONIA

To the Editor: The editorial "Influenza and Pneumonia" in the December 9 issue of the *Journal* is timely and appropriate, but by implication it perpetuates an error when it states "A most significant downward trend in the figures began in the early 1930's, when specific serum treatment for many types of pneumonia was introduced." The figures for Massachusetts, where an intensive serum program was conducted in the 1930's, do not show any downward trend in that decade until 1938, after the use of chemotherapy became widespread. As a matter of fact the Massachusetts figure for 1936 (96.3) is higher than that for 1930 (95.0), and back in 1927 it had dipped to 97.5.

All that we are ever likely to know about the serum treatment of pneumonia is now recorded. It is too bad to let these legends continue, as a profession we do not need to be flattered and do not wish to be falsely recorded by such implications in the history of medicine. I am convinced that a careful study of pneumonia between 1920 and 1937 will fail to reveal any one circumstance that satisfactorily explains the reduction of mortality, it is extremely doubtful that our bedside practices had anything to do with it. Personally, I was never convinced that the serums we used in the 1930's were any more effective than those available for the more common types in 1920. Certainly, we have no evidence that any of them compare with the chemical and biologic agents of the past decade.

DWIGHT O'HARA, M D

Waltham, Massachusetts

NOTE A previous editorial, entitled "Pneumococcal Pneumonia," which appeared in the April 17, 1947, issue of the *Journal*, had already taken cognizance of the facts that Dr O'Hara's letter re-emphasizes. The reference to the figures quoted in the recent editorial was for industrial policyholders from the country as a whole as compiled by the statisticians of the Metropolitan Life Insurance Company. In these figures the temporal if not the causal relation of the drop in pneumonia mortality to the use of serums was implied. The beneficial effects of antipneumococcal serums, particularly those prepared in rabbits and available just prior to the introduction of effective sulfonamides, now constitute only a matter of historical interest. It should be pointed out, however, that much firmer convictions are held by most of those with considerable and intimate experience with the use of serums in large numbers of cases. Regarding the effects on the mortality statistics for Massachusetts, too many factors are involved in the compilations of such figures to warrant any serious interpretations, controversies or comparisons with carefully studied clinical material compiled by competent observers. — Ed

A CORRECTION

To the Editor I appreciate very much the honor of the editorial comment in the December 9 issue of the *Journal*. I would, however, like to make two minor corrections and add a note.

My college class was 1908, 1911 for my medical class was correct.

The decoration of the Order of the White Lion was given in 1946 to all the members of the American Medical Mission to Czechoslovakia under the auspices of the Unitarian Service Committee in acknowledgment of the helpful work in restoring the medical friendship and co-operation of the two countries. Among those in Boston receiving the decoration were Drs Joseph Aub, Otto Krayner, Joseph Volker and Joseph Lazansky. At the time of my visit to Prague in April, 1948, I was on my way to another American Medical Mission of the Unitarian Service Committee, this time to Greece and Italy, in which I was associated with ten other doctors, including several more from Boston — namely Drs Chester Jones, Reidar Sognnaes and Herman DeWilde. I spent a few days in Prague (en route to Athens) to attend the six hundredth anniversary of Charles University, the oldest university in Central Europe, in acknowledgment of the past accomplishments of that great institution. Professor René Leriche, of France, and I received honorary doctorates from the faculty of medicine. Other medical candidates were not present, but honorary degrees were bestowed by other faculties on other foreign guests.

In my new role as adviser of the National Heart Institute and executive director of the National Advisory Heart Council I shall continue to reside in New England and to practice medicine half time, following patients whom I have seen in the past. Adjoining my own private office at 264 Beacon Street is a branch office of the National Heart Institute, one of the National Institutes of Health under the United States Public Health Service whose headquarters are at Bethesda, Maryland.

PAUL D WHITE, M D

Boston, Massachusetts

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Practice of Allergy. By Warren T Vaughan, M D. Revised by J Harvey Black, M D. 4th, cloth, 1132 pp, with 333 illustrations and 81 tables. Second edition. Saint Louis: The C V Mosby Company, 1948. \$15.00.

This treatise, first published in 1939 by Dr Vaughan, has been revised for the second edition by Dr Black, who assumed the authorship after the death of Dr Vaughan. The text has been revised to bring the subject up to date. The chapters on fungous infection with associated allergy and on vital capacity have been rewritten. A large bibliography follows the text, and a comprehensive index concludes the volume. The type and printing are excellent, but the use of a coated paper makes the volume very heavy. This encyclopedic treatise is recommended for all medical libraries and to all specialists in its field.

Pioneer Life in Kentucky, 1785-1800. By Daniel Drake, M D. Edited from the original manuscript, with introductory comments and a biographical sketch by Emmet F Horine, M D. 8th, cloth, 257 pp, with 8 illustrations and frontispiece. New York: Henry Schuman, 1948. \$4.00.

The letters of Dr Daniel Drake, edited by his son, Charles Daniel Drake, were first published in 1870. The letters were republished in 1907, and both editions have long been out of print. In an examination and comparison of the original letters, now in the library of the Cincinnati General Hospital, with the published letters, Dr Horine found many discrepancies and omissions. It was found that Dr Charles Drake took many liberties with his father's letters in an attempt to improve their literary style. In this edition the letters have been faithfully reproduced in Dr Drake's phraseology from the original manuscript letters. Dr Daniel Drake was a pioneer western physician, the first medical student of Cincinnati and a professor at Transylvania University at Lexington, Kentucky, in 1817. He was prominent in Ohio affairs, establishing the Medical College of Ohio, the Western Museum, the Cincinnati College and the *Western Journal of the Medical and Physical Sciences*, of which periodical he was editor from 1827 to 1838. This important book should be in all medical and general historical collections.

Treatment of Heart Disease. By William A. Abrams, M S, M D, Ph D. Associate professor of medicine, Northwestern University Medical School and attending physician, Michael Reese Hospital, Chicago. 8th, cloth, 195 pp, with 11 illustrations. Philadelphia: W B Saunders Company, 1948. \$3.50.

This monograph has been written for the general practitioner and medical student as a systematic and practical guide in the treatment of heart disease. It reflects the experience of the author gained in teaching and in private practice and consultation work and does not include methods of treatment used by other heart specialists. The material offered is confined to therapy and does not discuss etiology, symptomatology and diagnosis. A comparatively large amount of space is devoted to congestive heart failure because the author believes that the majority of persons with almost any form of organic heart disease ultimately develop this condition. The first chapter discusses the pharmacologic action of drugs used in treatment, followed by chapters on the various heart diseases. The text is well printed with a good type. The use of a coated paper is not justified by the number of illustrations. A long bibliography concludes the text and there is a good index.

A History of the Heart and the Circulation. By Frederick A. Willius, M D, M S in Med, senior consultant in cardiology, Mayo Clinic, professor of medicine Mayo Foundation for Medical Education and Research Graduate School, University of Minnesota and Thomas J. Dry, M A, M B, Ch B, M S in Med, consultant, section on cardiology, Mayo

Chinc, associate professor of medicine, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota 8°, cloth, 456 pp., with 170 illustrations Philadelphia W B Saunders Company, 1948 \$8 00

This new history of the heart and circulation is divided into three parts. The first presents a chronologic history from 5000 B C to 1925 A D, arranged by periods. The second consists of twenty special biographies of pioneers in various aspects of the subject, from Hippocrates (c 460-c 377 B C), to Sir Thomas Lewis (1881-1945). The third is a chronologic presentation according to subjects. To each chapter there is appended an extensive bibliography. Two good indexes of authors and subjects conclude the volume. The text is well written in a seminarrative style and is illustrated with portraits of physicians discussed in the text. The chronologic tables in the third part should prove very valuable for reference purposes. The book should be in all medical-history collections and in all medical libraries, both small and large.

Diagnostic Procedures for Virus and Rickettsial Diseases Published by The American Public Health Association 8°, cloth, 352 pp., with 20 illustrations New York American Public Health Association, 1948 \$4 00

This book is the joint work of the members of a special committee of the American Public Health Association. Seventeen diseases are discussed by authorities on the various diseases. Laboratory methods applicable to the various diseases are described in the chapters dealing with the diseases. A good index concludes the volume, which is well published. It should be in all medical libraries and medical laboratories.

The Salicylates A critical bibliographic review By Martin Gross, M D, research assistant (assistant professor), Laboratory of Applied Physiology, Yale University School of Medicine, and Leon A Greenberg, Ph D, associate professor in applied physiology, Yale University School of Medicine. With an introduction by Howard W Haggard, M D, director, Laboratory of Applied Physiology, Yale University School of Medicine 8°, cloth, 380 pp., with 20 illustrations and 29 tables New Haven Hillhouse Press, 1948 \$6 00

This monograph is one of a series projected by the Institute for the Study of Analgesic and Sedative Drugs. The volume on acetanilid was published in 1946. The literature reviewed 4093 titles, and the bibliography uses 173 pages of the book. The first part of the work analyzes and reviews the chemistry, physiology, pharmacology, toxicology and therapeutic uses of the salicylates. The text is well printed with a good type on light paper. An index of subjects concludes the volume. The book is recommended as a reference source for all medical libraries.

The Frightened Child By Dana Lvov 8°, cloth, 186 pp New York Harper and Brothers, 1948 \$2 50

This novel with a psychologic trend has a physician as one of its characters.

Your Skin and Its Care By Howard T Behrman, M D, and Oscar L Levin, M D 12°, cloth, 255 pp., with 11 illustrations New York Emerson Books, Incorporated, 1948 \$2 50

This manual is written for the laity and is devoted to the hygiene of the skin in health and disease, with chapters on the hair, sebaceous glands and quackery in relation to dermatology. The material is well arranged, and the text well written in a simple manner. A glossary of terms concludes the text. There is a good index. The volume is a good example of a popular medical manual.

NOTICES

ANNOUNCEMENT

Dr Robert R Commons announces the opening of his office for the practice of internal medicine at 121 North San Vincente Boulevard, Beverly Hills, California.

NEW ENGLAND HEART ASSOCIATION

A meeting of the New England Heart Association will be held in the Auditorium, Boston University School of Medicine, 80 East Concord Street, on Monday, February 14, at 8 15 p m, Dr Robert W Wilkins presiding.

PROGRAM

Observations on Normal and Pathologic Physiology of Postarteriolar Vascular Beds in the Human Forearm and Calf Drs J Litter and R W Wilkins
The Relative Velocity of Plasma and Cells in the Circulation of Man Drs C P Emerson, E D Freis and J R Stanton
Prognosis for Surgically Treated Hypertensive Patients. Dr F H Smithwick
Comparative Hemodynamic Effects of Small Intravenous Doses of Epinephrine in Normotensive Subjects and in Hypertensive Patients before and after Sympathectomy Drs W E Judson, C M Tinsley and J W Culbertson.
A Case of Pheochromocytoma Extensively Studied before and after Surgical Removal Drs R W Wilkins, W E Greer, J W Culbertson, C H Burnett, M H Halpern, J Litter and R H Smithwick

Interested physicians and medical students are cordially invited to attend.

MASSACHUSETTS MEDICO-LEGAL SOCIETY

The winter meeting of the Massachusetts Medico-Legal Society will be held in the Department of Legal Medicine, Building E-1, Harvard Medical School, on Wednesday, February 9, at 2 30 p m.

PROGRAM

When to Accept Jurisdiction Dr Richard Ford
The Medical Examiner's View Dr Timothy Leary
Unusual Medicolegal Problems Dr Alan R Montz
Establishment of identity and time, cause and manner of death of unknown person twelve years after death.
The benefits of a second autopsy after three years in a wet grave
Business Meeting
Refreshments

HELEN PUTNAM FELLOWSHIP

The Helen Putnam fellowship for advanced research in genetics or mental health, open to women scholars who have their doctorate or who possess equivalent qualifications, will be offered by Radcliffe College for the academic year 1949-1950. The award carries a stipend of \$2600 a year with the possibility of renewal.

Applicants are asked to submit a plan of research, and preference will be given to those whose research is already in progress.

Applications should be returned to the Secretary of the Graduate School, Radcliffe College, not later than April 1.

SOCIETY MEETINGS AND CONFERENCES

JANUARY 7-APRIL 13 American College of Surgeons. Sectional Meetings. Page xi issue of December 23.

FEBRUARY 6 National Conference on Medical Service. Page 80 issue of January 13.

FEBRUARY 9 Massachusetts Medico-Legal Society. Notice above.
FEBRUARY 10 Endoscopy—Its Indications and Limitations. Dr Edward B Benedict. Pentucket Association of Physicians. 8 30 p m. Haverhill.

FEBRUARY 14 New England Heart Association. Notice above.
MARCH 7-9 American Academy of General Practice. Page 728 issue of November 4.

MARCH 28-APRIL 1 American College of Physicians. Page 158 issue of July 22.

MAY 4 New England Obstetrical and Gynecological Society. Springfield Country Club Springfield.

MAY 16-19 American Urological Association. Biltmore Hotel Los Angeles California.

MAY 24-26 Massachusetts Medical Society. Annual Meeting Worcester Memorial Auditorium Worcester.

MAY 26-28 American Gopher Association. Hotel Lorraine Madison Wisconsin.

(Notices concluded on page xiii)

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Number 5

FURTHER EXPERIENCES WITH INJURED BILE DUCTS*

A New Method of Repair

FRANK H. LAHEY, M.D.†

BOSTON

EARLY in my surgical experience I became interested in the problem of injuries to the bile ducts and in 1923 wrote my first paper^{1, 2} on this subject, dealing with the results obtained by transplanting completely external fistulas when common and hepatic ducts had been so injured and severed that all or practically all the bile was discharged ex-

Since that time we in the clinic have had a continuing interest in the problem of the management of the patients with strictures of the common duct and defects in the common and hepatic ducts from excising sections of them.

We have operated upon 227 patients for benign strictures of the bile ducts. There have been 27

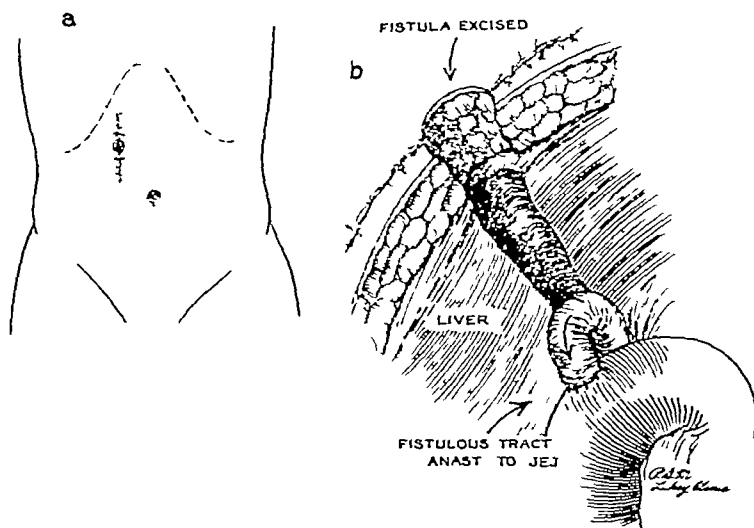


FIGURE 1 Transplantation of Completely External Fistula

This illustration (b) diagrammatically shows a completely external biliary fistula cored from its bed in the liver and transplanted into a loop of jejunum brought up anterior to the transverse colon. In insert a may be seen the tissue to be cored out of the abdominal wall to preserve the fistulous tract. (As stated in the text, this procedure has not proved satisfactory in terms of permanent patency.)

ternally. This operation was first proposed and employed on a patient by Dr. Hugh Williams at the Massachusetts General Hospital (Fig. 1).

*Presented at the annual meeting of the New England Surgical Society, New Haven, Connecticut, October 1, 1948.
†From the Department of Surgery, Lahey Clinic.
†Director, Lahey Clinic.

hospital deaths in the entire series, an over-all mortality of 11.9 per cent. Of the 227 cases, 139 have been done since 1943, with 12 deaths, a mortality for this period of 8.6 per cent. In this experience we have employed nearly every known type of surgical approach to the problem, and Dr. Cattell and I

have now developed one that when it can be employed, as it can in most of the cases, offers the best prospect of a lasting, satisfactory result of all the measures of which we know. This method will later be published in a journal devoted entirely to surgery, but will be described in the latter part of this article in enough detail so that it will be available for any surgeon who might care to use it. These strictures have varied greatly in character, as well as in the number of previous operations the patients have had before coming to us, 2 examples of which are presented below, and they have likewise varied greatly in the measures employed in the attempt to restore the flow of bile into the intestinal tract. They have been complicated lesions and, in many cases, unsatisfactory to deal with. When one realizes, however, that portal cirrhosis or failing liver function (which is due to the biliary back pressure from stricture and the superimposed cholangitis so frequently associated with this lesion) will eventually result in death in all these cases unless something is done, it can be understood that however unsatisfactory many of these cases are, we must still endeavor to handle them surgically. This is done in an attempt to restore the patients, as can be done in some cases, to complete health and in others to be satisfied with merely prolonging their lives and making an unsatisfactory state a little more satisfactory than it would otherwise be.

CASE REPORTS

CASE 1 This patient had had a cholecystectomy in October, 1943. She had two repairs of her common duct, in 1943 and in 1944. In the latter part of 1944 a T-tube was inserted in her hepatic duct and in her common duct. She managed to get along with the T-tube until 1947, when she again became jaundiced and was operated on again, with the insertion of another T-tube. This T-tube passed down the common duct and into the duodenum in 3 months. In January, 1948, another T-tube was inserted, but in spite of this, it became blocked and this patient came to us for repair of her duct. (There had thus been six previous operations on the biliary tract of the patient before she came to the clinic.)

The patient was operated on by me on July 14, 1948. The hepatic duct was found with almost no cuff remaining, — that is, almost all the common hepatic duct had been destroyed, — and a Y-tube was inserted into the two limbs of the hepatic duct with less than 1 cm. of hepatic duct remaining. To this the mobilized demonstrated common duct, which had been freed from the pancreas and from behind the duodenum, was anastomosed, with at least for this brief time complete and satisfactory restoration of flow of bile into the intestinal tract. It is, of course, distinctly possible that an obstruction will again occur, but this experience does demonstrate how complicated these cases can be and yet how possible it is in many of them to re-establish the bile flow in spite of many (in this case, six) previous operations elsewhere upon the biliary tract.

CASE 2 This case likewise illustrates how complicated these cases may be. The patient had a cholecystectomy in 1947, at which time, either as a result of the acute gall-bladder condition for which the cholecystectomy was done or because of injury to the duct, a stricture resulted. Within the same year she was operated on again, and an anastomosis of the hepatic duct into the duodenum was done. This failed to function, and a further operation was done, again anastomosing the hepatic duct to the duodenum.

When this patient came to the clinic she was deeply jaundiced, and had had chills and fever for 2 months.

The hepatic duct was found with but a short stump. It was anastomosed to the common duct mobilized from the pancreas and behind the duodenum. After this anastomosis the patient became jaundiced, and a subdiaphragmatic abscess developed, which required drainage, but the jaundice failed to clear. She was sent home to die, with the idea that no more could be done. A further accumulation of the subdiaphragmatic abscess ruptured through the bronchus, and bile was discharged through the bronchus. A communication from her physician reported that it did not seem possible that she could recover.

Recent communications have indicated that the bronchial fistula has closed, bile is now draining into the intestinal tract, jaundice has cleared, and the patient appears to be at least temporarily recovering.

DISCUSSION

These cases are but illustrations of how complicated these problems can be and demonstrate some of the undesirable events that can be associated with the management of these extremely difficult problems.

This not inconsiderable experience with the management of injuries to the bile ducts has resulted in our arriving at quite definite convictions concerning what can and cannot be done and what can be expected with the various procedures that we have employed.

I should like to list in the sequence of their development the various measures that we and others have employed in the management of strictures of the bile ducts and to make comments on our satisfaction or dissatisfaction with each of them and particularly to mention, when we are dissatisfied, why dissatisfaction with the method has arisen.

This article attempts only to present the various types of operative procedures employed for the various conditions and to illustrate them diagrammatically.

It is my hope in presenting this experience of one surgical group with such a considerable number of these trying cases that I can at least bring up to date what has gone on in our experience and the plans for their management and discuss the futility of some of the plans that we and others have employed, with the reasons why we think they do not work, and present a new method that we have now used in enough cases and over a long enough period so that we can say that, when it is possible, it offers the best opportunity to obtain a satisfactory and lasting result.

The first plan of management of injuries to the bile ducts, that of transplantation of cored-out biliary fistulas, illustrated diagrammatically in Figure 1, was unsound in principle.

Although it is possible to transplant an external biliary fistula successfully into the jejunum or stomach, it can almost be said with certainty that at least in a predominating number of the cases, even though the fistula transplant is successful, it will ultimately contract, seal off and result in suppression of bile. It has been our experience with external fistulas that have been converted into internal fistulas by implantation into the stomach or

jejunum, and likewise with external fistulas that remain external, that the contraction of cicatricial tissue forming the wall of the sinus will ultimately be greater than the secretory pressure of bile, which in the beginning keeps it open, and that this will eventually, in either an external biliary fistula or an internal biliary fistula owing to an injury to the common or hepatic bile duct, result in spontaneous closure of the fistula.

External biliary fistulas made directly from the gall bladder in the presence of a stone or obstruction below the point of entrance of the cystic duct into the common or hepatic duct will of course, in most

accurate end-to-end anastomosis, it will result in permanent and satisfactory drainage of bile into the intestinal tract. Unfortunately, ascending infection, with resulting chills and fever and the ultimate development of cirrhosis, has occurred in too many of these cases to make it a satisfactory type of procedure. In addition, too many of these anastomoses however accurately they may be done in the beginning later contract and cicatrize down to the point where obstruction results. I have personally disconnected a number of such anastomoses done elsewhere that have contracted and

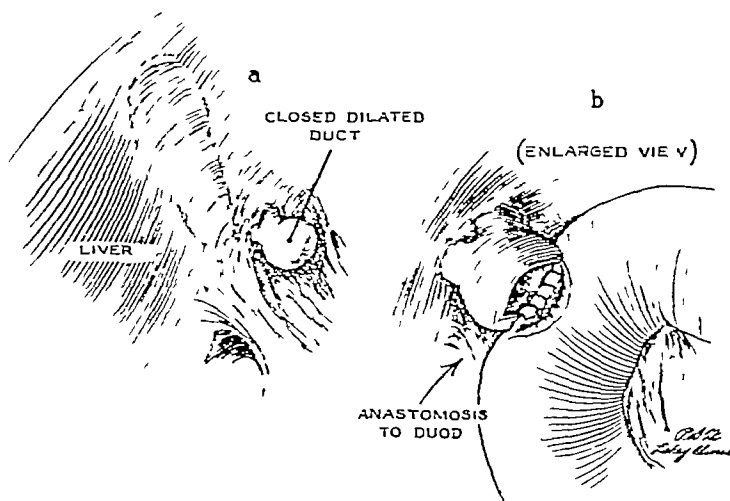


FIGURE 2 *Anastomosis of Dilated End of Cat Hepatic Duct to Duodenum or Jejunum*
The closed and dilated end of a cat hepatic duct is shown in a. The end has sealed over and complete obstruction has resulted. In b is shown the end-to-side anastomosis of the dilated and closed end of the hepatic duct to a loop of jejunum brought up over the transverse colon. Note how accurately mucosa-to-mucosa anastomosis can be done. (These structures are shown in enlarged detail to make them clearer.)

cases, drain on indefinitely because this is a mucous-membrane-lined fistula. When however a fistulous tract runs from the hilus of the liver at the region of the hepatic and common ducts after removal of the gall bladder and injury to the main bile ducts its length of cicatricial lined walls is so great that constriction with obliteration of the fistulous tract will result in almost every case. It is for this reason that this operation has been abandoned and is, we believe largely without value.

The next type of management of the patient with an injury to the hepatic or common duct resulting in an external biliary fistula and popularized by W. J. Mayo has been the direct mucosa-to-mucosa anastomosis (Fig. 2) of the dilated end of the cut hepatic duct to the duodenum or jejunum. If this operation, which is not difficult when the dilated end of jejunum is of considerable size, is done with

resulted in jaundice the patients coming to us for further repair and of a different type.

There have been a number of plans devised to overcome the ascending infection in repairs of this type one being the 'Y' loop in which something over a foot of blind jejunum is anastomosed to the end of the hepatic duct inserting the proximal loop of jejunum below this level to avoid ascending infection. Another suggestion has been the introduction of infolds in this segregated loop to discourage the ascent of jejunal contents through the anastomosed area to bring about infection. Still a final proposal has been the establishment of an entero-enterostomy below the point of the anastomosis of the end of the hepatic duct to the jejunum to side-track most of the contents of the jejunum and thus avoid ascending infection in the gall bladder.

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As the result of this experience with rubber and vitallium tubes and, in addition, tubes of bouncing clay introduced to bridge the gap when sections of the hepatic and common ducts have been injured or removed, it is our belief that when they must be introduced one must assume that certainly in most cases they will eventually plug and later require removal and replacement.

The next proposal in order of sequence was that suggested by Dr Arthur W. Allen² in 1944—that is, the employment of a turned-in, single loop of jejunum to anastomose to the hilus of the liver about the cut end of the hepatic duct (Fig 4). Although we have had no experience with this operative procedure, we have little hope but that what happens with cut hepatic ducts will happen when the end of the hepatic duct is implanted in the turned-in end of a loop of jejunum: the end of the duct will cicatrize, close and result again in complete obstructive jaundice. I have had the opportunity to disconnect one of these, which had been done in another part of the country, and found that this was what had taken place. We have seen so many of these patients who come to us

of at the last meeting of the American Surgical Society by Dr Alfred Blalock, is the anastomosis of the amputated end of the left lobe of the liver to the jejunum in the hope that the drainage from the right hepatic duct can be backed up along the left hepatic duct and that, by means of this reversed flow of bile through the left hepatic duct, the entire right and left lobes of the liver can have

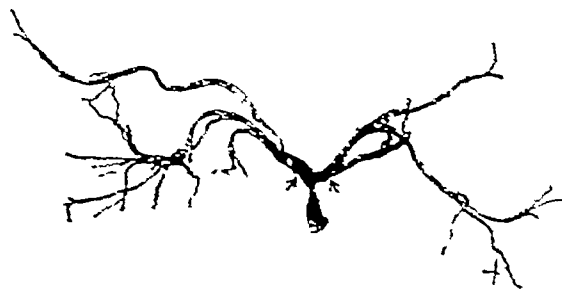


FIGURE 6 Corrosion Specimen of the Bile Ducts in Which Plastic Material Is Introduced into the Bile Duct and the Lesser Perichyma Digested

In such specimens it may be observed that the biliary passages of the left lobe of the liver are quite complete and separate from the right lobe and probably, considerably without connection. As stated in the text and shown in Figure 5, unless enough hepatic duct remains uninjured, bile cannot descend from the right duct up the left, and as stated in the text when enough hepatic duct remains to permit this it is possible in most of the cases by the plan here presented to anastomose the mobilized common duct directly to the stump of the hepatic duct and thus to retain the sphincter and obtain mucosa-to-mucosa healing.

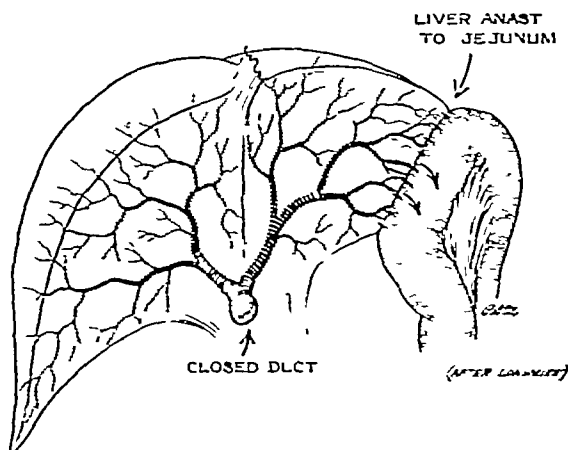


FIGURE 5 Plan of Amputating a Portion of the Left Lobe of the Liver and Anastomosing It Directly to a Loop of Jejunum in the Hope That the Bile from the Right Lobe Will Descend the Right Hepatic Duct, Ascend the Left Hepatic Duct, and Thus Drain Directly into the Jejunum

Note the closed end of the hepatic duct, which may be long enough to permit bile to come down the right hepatic duct and up the left hepatic duct to make this procedure feasible.

after having had several previous operations in whom only a scarred intrahepatic short stump of common hepatic duct remained that we are very skeptical that the suture of this loop of jejunum about the open duct will result in permanent patency of the end of the hepatic duct in the presence of so much scar tissue in its walls.

A recent novel proposal made by Dr W. P. Longmire, Jr., of Johns Hopkins Hospital, and spoken

their biliary drainage discharged into the jejunum (Fig 5 and 6).

We do not have much hope for the success that may follow this procedure because as we have seen them in so many of these cases, as shown in Figure 5, the common hepatic duct will have been destroyed up to the point where the two main hepatic ducts draining the right and left lobes of the liver (Fig 6) will be all that remains of the hepatic ducts.

Dr W. A. Meissner, of the pathological laboratory of the New England Deaconess Hospital, has made corrosion specimens of the hepatic ducts of livers for us, and if one sees these it will be evident that for this proposal to function it would be necessary that there be a fair length of common hepatic duct into which the right hepatic could discharge and then pass up in the reverse direction to the left hepatic duct (Fig 6). We know from our experience in operating on so many of these patients that this is often not the case and that, as mentioned above, the loss of substance of the hepatic duct, with the multiple operations that many of these patients had had, has been so great that little or no common hepatic duct remains and so there is no communication that can be employed between the right and

None of these plans have been satisfactory, and one can only say that although these types of anastomoses do drain bile, in most of the cases the results are seriously compromised by the repeated attacks of cholangitis that accompany them.

The next stage in the development of the surgical management of injuries to and strictures of the hepatic and common duct was the introduction of

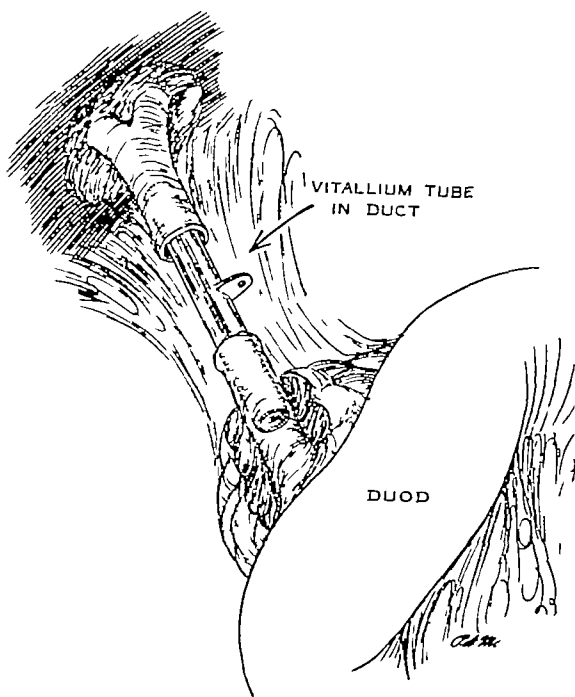


FIGURE 3 Plan of Introducing a Vitallium Tube, as Shown in This Case, but in Others Sections of Rubber Tube or the Material Called Bouncing Clay Have Been Employed, the Tube Serving as a Substitute for the Lost Segment of the Common or Hepatic Duct

It is to be recalled that the scar tissue about this tube is wrapped around the tube to enclose it tightly and in the hope that it will be supported as a substitute for the missing section of duct. Note the projecting tab on the vitallium tube, which recalls that these tubes have passed completely through the common duct, through the sphincter of Oddi into the duodenum, in spite of the presence of such an offshoot that one would expect would hold the tube in place permanently.

segments of rubber or vitallium tube, as shown in Figure 3, the upper end being introduced into the stump of the hepatic duct, the lower end into the stump of the common duct and such material in the form of scar tissue and omentum as could be obtained wrapped around the missing segment to provide covering for the implanted tube within the two cut ends of the ducts.

The drawbacks to this procedure have been two in most cases the tube has been passed in spite of the use of all types of tubes in attempts to make them remain in place—whenever the tube has been passed, it has been our experience that in practically all cases the remaining cicatrized area, unlined with

mucosa as it is, no longer stays open but eventually, as does the external biliary fistula, contracts, closes and again produces complete biliary obstruction, in addition, many of these tubes, even though they remain in place, eventually become plugged and require removal and the reinsertion of another tube. As many as four different tubes have been introduced in some of our patients on whom this procedure was employed, the periods varying from one to three years. The longest period a tube, introduced in such a case with a complete defect between the cut end of the hepatic duct and the common duct, has drained without jaundice has been seven years. This patient eventually died of cirrhosis, at autopsy the tube was found plugged, and in all probability the tube had plugged early, and bile was being passed satisfactorily around it.

Soon after this the employment of a vitallium tube in place of rubber tubes was proposed in the hope that because vitallium is well tolerated by the tissue, being a nonelectrolytic metal, these tubes would not plug. It was hoped that these tubes (Fig 3), which possess a tab or flange sticking out from their longitudinal wall, would not be passed into the duodenum. Neither of these hopes has been fulfilled. Vitallium tubes have, in our experience, plugged just about as often as have rubber tubes, and, surprising as it may seem, the

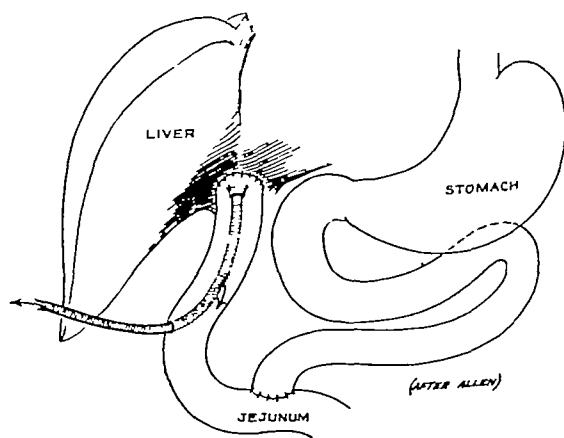


FIGURE 4 Method of Employing a "Y" Loop of Defunctionalized Jejunum, the End of Which Has Been Turned in and Sutured to the Hilus of the Liver about the Opening into the Cut End of the Hepatic Duct

vitallium tubes even with the good-sized flange that is attached to them have several times passed through the common duct, through the sphincter of Oddi into the duodenum and stricturing of the segment that they replaced has followed in most of the cases in which the tube has passed. Furthermore, like rubber tubes, many of these vitallium tubes have had to be removed and replaced because of their being plugged.

patency of the sutured duct. We have left these T-tubes in place up to a year and longer in certain cases, to ensure patency at the line of suture and to permit good union of the mucosal surfaces. We have now for a considerable period introduced these T-tubes through a slit either in the hepatic duct above the line of anastomosis when the hepatic duct is sufficiently long or through the common duct below the line of suture when the hepatic duct is short (Fig 7). This permits one limb of the tube to pass through the point of sutured duct and permits the withdrawal at the end of a year of the

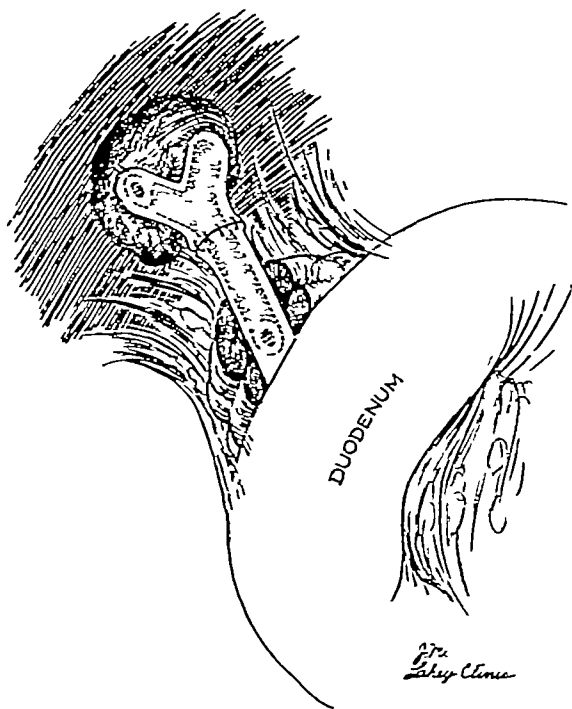


FIGURE 8 Diagrammatic Illustration Demonstrating How It Is Necessary to Employ a Y-Tube with One Limb in the Right and One in the Left Branch of the Hepatic Duct to Make Complete Anastomosis Possible

In many of these cases it has not been possible to introduce a T-tube below because it would be necessary to place the upper limb of the T-tube in either the left or the right hepatic duct. This line of procedure has the disadvantage of requiring that the tube be left in place, with the possibility and not improbability that it will later plug and require replacement. In the corrosion specimen (Fig 6) arrows have been placed on the right and left hepatic ducts to indicate the height to which destruction of the hepatic ducts has taken place in many of the patients who have been subjected to repeated attempts to repair the ducts

T-tube without injury to the line of anastomosis or without producing the narrowing that occurred when cicatrization of the aperture took place at the point of the tube withdrawn through the suture line.

In the management of complicated bile-duct problems of this sort many of these patients have had so many previous unsuccessful attempts at

repair that no hepatic duct at all remains. In such cases it has been necessary to introduce a small section of Y-tubing with one limb in each intra-hepatic duct, the other passing down into the mobilized common duct, and to do a direct anasto-



FIGURE 9 Plain Film of the Abdomen in a Case in Which It Was Necessary to Implant a Y-Tube (of Boring Clay), As Shown Diagrammatically in Figure 8

mosis about it on the indwelling tube (Fig 8 and 9).

This is less desirable than the introduction of a T-tube for a year because if blockage of the indwelling T-tube occurs it can frequently be overcome by the introduction of ether or by irrigation with saline solution. We have had relatively little trouble with the T-tube blocking, but when one leaves a Y-tube in, as shown in Figure 8, with no external drainage, there are often cases in which plugging of the tube occurs, and re-operation becomes necessary if another tube is introduced to bring about maintenance of drainage.

In doing these end-to-end anastomoses all sorts of unsatisfactory conditions are bound to arise. An occasional result in our experience — and one about which we know of nothing to do — is that in which the lower end of the duct can be found but is of such small, atrophic character that it is impossible even after it has been mobilized to dilate it up to a size adequate for the introduction of a T-tube of satisfactory caliber. In still other cases there will be so much destruction and scarring of the pancreas, the common duct and the region about the duodenum that it will — very rarely in-

left hepatic ducts by means of which bile from the right lobe of the liver could be made to ascend through the left hepatic duct and thus discharge into the intestine as the cut end of the left hepatic duct in the severed left lobe of the liver is implanted into the jejunum

We are very skeptical that this ingenious proposal will be of any great value. We believe that it could

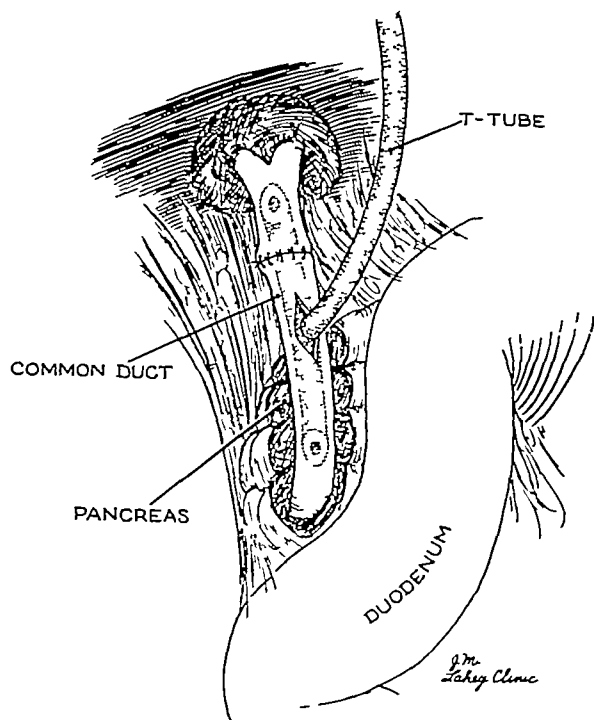


FIGURE 7 Plan Devised by Drs Cattell and Lahey, with the Duodenum Rolled to One Side, the Pancreas Split, the Retro-duodenal and Intrapancreatic Common Duct Exposed Mobilized and Approximated to the Stump of the Hepatic Duct

Note the demonstration of the intrahepatic portion of the duct and, in addition, the method of introducing a T-tube through an incision in the common duct below the line of suture so that one limb extends through the anastomosis and the anastomosis can be made accurately and completely around the entire circumference of the duct. Note also, diagrammatically, how often it is necessary by means of fulguration to dissect the scarred end of the hepatic duct out of the hilus of the liver and in many cases to carry the dissection up sufficiently so that both individual hepatic ducts, right and left, are demonstrated

work only when an adequate stump of hepatic duct remains, as shown in Figure 6, and, even then, we believe that the proposal of direct duct anastomosis, which was devised by Dr Cattell and myself and which is discussed below, will then be a possible and much more satisfactory approach to the problem

In seeking for a method that offered more satisfactory prospects of restoring the excised or damaged common and hepatic ducts to normal and thus the discharge of bile in the duodenum by a normal channel, we have visualized two things that would be

necessary to bring about satisfactory function in the discharge of bile from the biliary radicals in the liver into the duodenum. One, outstandingly, is the necessity for the preservation and functioning of the sphincter of Oddi. It is only by the preservation of this apparatus that one can be assured of the absence of ascending infection, chills and jaundice and their effect upon the liver itself. The other requirement is that permanent restoration of the main bile channels can be accomplished only by direct end-to-end anastomosis of the injured or severed duct so that there is accurate mucosa-to-mucosa approximation, as is necessary in restoration of any of the mucous-membrane-lined structures in the body that convey either fluid or liquid

In the course of a large experience with mobilization of the duodenum and demonstration of the lower end of the common duct where it passes through the head of the pancreas and into the duodenum as part of removing the duodenum and duodenal ulcers within the duodenum adherent to the bile ducts, we have learned to mobilize the duodenum by mobilizing its external wall and to demonstrate the portion of the common duct behind the duodenum and within the pancreas by splitting the pancreas about the common duct. This directed our attention to the possibility of mobilizing this portion of the common duct, which by its location within the head of the pancreas and behind the duodenum, is usually protected from injury no matter how many operations are done for repairs on cut or crushed ducts

It was through familiarity with this procedure and with Dr Cattell's experience with resections of the pancreas that we became interested in so mobilizing the duodenum and so visualizing the lower end of the common duct behind the duodenum and in the head of the pancreas that when an adequate amount of hepatic-duct stump remains, as it usually does, direct end-to-end anastomosis could be accomplished

This procedure has now been done in 43 cases over five years, and we have deferred reporting it as a method until we had had enough experience with it to suggest its possibility and be certain of its feasibility in at least a very high percentage of cases of injury or stricture of the common and hepatic ducts

It is surprising, when the uninjured portion of the common duct that runs through the pancreas to enter the back of the duodenum is mobilized and delivered from its oblique position behind the duodenum, how often this end can be made to approximate to the end of the hepatic duct without tension, even when a considerable portion of the common or hepatic duct has been destroyed (Fig 7)

When we first did these duct anastomoses the T-tube was brought out directly through the line of anastomosis. We have considered it necessary in these cases to introduce such a tube to maintain

hospitals after the war and that a major reorganization of the conditions of medical practice would be needed. Conferences between the medical profession and the Minister of Health in Mr Winston Churchill's Coalition Government resulted in tentative agreement for the provision under the auspices of the Minister of Health of a service to cover all aspects of medical care for almost the whole nation.

The general election of 1945 placed the Labour Party in power, and this agreement was ostensibly scrapped by the new minister of health, Mr Aneurin Bevan. He announced that he would present a measure to Parliament without bothering to have full discussion with any representative of the British Medical Association, and the dispute with the British medical profession that resulted has received wide publicity. It was a foregone conclusion, however, even three and a half years ago before Mr Bevan took over, that the central government would be in control of the conditions of medical practice. All the major hospitals have continued to receive indispensable financial support from the Government since the war, the use of this money being subject to continuous governmental surveillance. By virtue of these facts the conditions under which consultant practice is carried on in hospitals have been but little changed since the latest act became operative on July 5. Hence this is not a premature point at which to judge the status of the physician and his hospital work in England. Further, since the general practitioner's type of panel practice for the past thirty-six years on over a third of the population was already extended during World War II to over half the population, one may extend these accumulated data to help in analyzing his present situation with almost the whole nation on some panel.

As was to be expected there were temporary dislocations and points of stress after medical care became completely free on July 5, but no mention has been made of these in the ensuing comments. The attempt has been to refer only to facts pertinent to the long-range trends. Some of the problems that have arisen are a consequence of current shortages and Government regulations in fields other than those strictly medical, these appear to present a more chronic, self-perpetuating source of trouble and are noted below.

The effects of the British National Health Service may be considered first from the standpoint of the general practitioner and secondly from that of the specialist, or consultant, as he is termed in England.

THE FAMILY DOCTOR

The physician in general practice in England today is swamped by a volume of work that makes it possible for him only rarely to take a clinical history or make a thorough physical examination in the fashion that is attempted in this country.

According to computations based on the experience with panel practice before the war, one may estimate that the British general practitioner must now in the course of a single day see in his office and in visits to homes an average of at least 50 patients if he has the average panel of 2000 persons — or 100 patients if he has the maximum panel of 4000. These figures are based on the knowledge that the prewar panel patients, largely men, each averaged five visits a year to their physicians¹ and on actuarial statistics^{2, 3} that demonstrate almost twice the morbidity in women who (as well as the men) are now insured in Great Britain. Such a staggering load permits the physicians but a few minutes with each patient. The tentative impression is that this expected volume of work is actually exceeded at present.

There is 1 physician per 875 inhabitants in Great Britain⁴ as compared with about 1 per 720⁵ in this country. The load in England appears to arise not from a great shortage of physicians there but because the physician is expected to carry out many functions that Americans would not consider a part of his task. Many people with minor complaints — inconsequential gastrointestinal upsets and upper respiratory infections — present themselves. Even though they may recognize the triviality of the disorder, they often wish to obtain medication, which is provided free of charge with the doctor's prescription, so that they sit about in his office and wait for a handout. This availability of free conversation with the doctor and free medicine also is considered to multiply the number of mild psychoneurotic and hypochondriac patients who appear.

The Labour Government's innumerable restrictions on the lives of every person also result in countless daily appeals to the doctor for escape. The employee may not be absent from work without a valid excuse, and a note from the physician is the easiest kind of justification to present. The worker tells his doctor that he has had diarrhea for two or three days and has not been at work, and the doctor signs a form he has ready for the occasion certifying to the man's illness. This has become such a standard practice that physicians have incurred the contempt of many employers, but the unhappy physician between the fires of labor and management will naturally accede to the laborer's wish. Otherwise, the patient may request a house visit the next time and present the doctor with the evidence for his complaint if it is bona fide, or he may change his name and with it his capitation fee per annum to another physician's list. And since labor is able to outvote management, the doctor's plight is likely to worsen rather than improve if he does not play this game. Many people who wish to evade the food-rationing restrictions seek a doctor's certificate of medical need for more eggs, meat, cheese, milk and so forth. There appears to be a limitless

deed, but occasionally — be impossible to find enough duct, even though it is completely mobilized, to get the ends together. Still another complication, which has been the most trying one we have had to deal with, is the fact that so often repeated, unsuccessful attempts at repair will have so destroyed the common hepatic duct that there will only be the separated intrahepatic right and left ducts. Even beyond this, Dr Cattell has successfully anastomosed the left hepatic duct when it was impossible to find the right because of the depth of scarred duct within the liver. In such cases atrophy of the right lobe and enlargement of the left have taken place, with adequate maintenance of liver function. Still another complication that has bothered us in these trying operations has been opening of the portal vein in the course of searching for either the lower end of the duct or the end of the hepatic duct within the hilus of the liver. In these cases we have successfully controlled such bleeding by suture of the portal vein, but this has resulted in the necessity of terminating at least temporarily further search for the duct.

SUMMARY

Experiences in the surgical management of 227 patients with benign strictures of or injuries to the bile ducts are presented. The development of the different methods employed since the publication of our first paper on the subject in 1923 is outlined, and the disadvantages of all these measures are discussed. A new plan, which has been employed for a minimum of five years in 43 cases, results in preservation of the sphincter of Oddi and direct mucosa-to-mucosa anastomosis when it can be employed and offers, it is believed, both the most logical approach to the surgical management of this up to now discouraging lesion and the best prospect of the permanent discharge of bile from the liver into the duodenum without complications that are involved with other procedures.

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RECENT IMPRESSIONS OF MEDICAL PRACTICE IN GREAT BRITAIN

WILLIAM H. SWEET, M.D.*

BOSTON

MANY physicians have hitherto regarded only with casual interest the controversy over the organization of medical practice in this country. I, myself, for example, have assumed that a faculty member of the staff of a teaching hospital could be little affected by any of the bruited changes — a notion that has been sharply challenged by observations of the current status of physicians in this and other categories in Great Britain. Severely jarred in my complacency by what I have seen during a recent period of work on one of the active services of a large English hospital, I am recording what are admittedly only a series of impressions rather than a careful statistical study. British physicians in all types of work have been profoundly affected by the legislation of His Majesty's Government, and we here would do well to realize that none of us are necessarily immune to the consequence of radical departures in medical administrative procedure.

The latest of the items of legislation governing medical practice in Great Britain finally came into force on July 5, 1948. It is important to recognize, however, that this is only the culminating step in a series of laws that began with the National Health Insurance Act, starting in 1912. This initial legis-

lation set up a system of compulsory health insurance for nearly all wage earners and resulted in the provision of the services of a general practitioner and of the medicines he prescribed for approximately a third of the population. No care of a medical specialist and no hospitalization were included in this measure. The Local Government Act of 1929 increased the number of hospital beds operated by the Government, and the Voluntary Hospitals Paying Patient Act of 1936 opened these institutions to the entire population whether able to pay or not. During World War II the bombing of civilians and large cities led to the construction by the British Government of numerous hospitals outside the cities and the employment either part time or full time of nearly all the physicians remaining outside the armed forces. The doctors were utilized in, and the hospitals were operated by, the British Emergency Medical Service under the Minister of Health. In addition to this organization the Ministry of Health during the war contributed notable financial support to the so-called voluntary or privately operated and endowed hospitals of the country, which included the major teaching hospitals of the medical schools. The wartime level of taxation and the rising costs of living made it apparent to all during the war that there would be insufficient voluntary donors to support the privately endowed

*Assistant professor of surgery, Harvard Medical School, lecturer in neurosurgery, Tufts College Medical School, associate visiting neurosurgeon, Massachusetts General Hospital.

of the area long after the physician had finished his postgraduate training in the hospital

Three years later the same consultant, now recognized as the most outstanding member of the medical faculty of his university, is like his colleagues working under many handicaps. His eminence led his university in 1944 to promise him an institute, to be erected forthwith as three temporary one-story buildings without basement, on empty space already available in the hospital grounds. By 1948 one of these has barely been started, the other two are less than half finished. Yet this is virtually the only hospital construction under way since the war in a city of a million inhabitants. The details of the numberless delays, which have already dragged out to over four years a construction that should have been a four-month task, furnish a monotonous account of the hamstringing of every energetic person by the requirement of a governmental permit for every item of material, for all the precursors of each of the materials, for the transportation of the precursors and the materials, for the allocation of the appropriate type of labor to handle the precursors of the materials, the materials and their actual construction and so on *ad nauseam*. These appear to be the advantages of completely centralized integrated control, so that first things can be done first. The activities of the most distinguished worker in this hospital continue to be carried on with the same primitive facilities that burden the remainder of the staff. All this is despite the fact that the Minister of Health has been for years in charge of all housing as well as hospital construction and might reasonably have been expected to provide for a little work on hospitals.

It is perhaps pertinent at this point to draw attention to the exclusive power of the Minister of Health under the present act to appoint all members of all medical boards governing all aspects of medical practice in the whole country, including the teaching hospitals. There is no grant *en bloc* of funds to units that otherwise remain independent of the Government, such as occurs now in relations between United States federal agencies and research groups, and represents the British method of support of its universities (entirely apart from the medical schools). Under a system in which the autonomy of the local group is preserved, tasks might well be completed in a reasonable time instead of dragging on in such a preposterous fashion for years.

The paucity of men of consultant status, serious before the war in England, has not been alleviated, despite the fact that increasing knowledge makes the need for them greater. The waiting list on the neurosurgical service on which I worked was such that a patient with a presumed brain tumor had to wait about three months before he could enter the hospital. Numbers die before they reach the top

of the list. There was virtually no time available to operate for the relief of pain on patients with malignant neoplasms — no matter how good their prognosis for a long useful life if free of pain.

The volume of nonmedical duties falling to the consultant, although not so overwhelming as that of the general practitioner, is still oppressive because all the factors creating such duties operate on him as well, albeit to a lesser degree. In the Regional Medical Board meetings the agenda drawn to my attention were largely cluttered with items of minor business administration, such as approving a new heating plant for an outlying hospital. To these the most senior and capable medical members of the community found themselves compelled to devote whole afternoons. I am told that they dare not resign from these boards, though, lest control be gained by men who would make the practice of medicine a series of acts of obedience to such fiat, proclamations, directives and commands as the board might see fit to dispense.

A minor example of the advantages of bureaucracy was my experience of applying to the appropriate segment of the Ministry of Health in Whitehall for certain special instruments to perform an operation by a hitherto untried method. The whole project was explained in some detail, and the letter of request received a prompt postal reply promising consideration. Eight months later, long after I had obtained the needed articles from a private source, I had a letter declining the request because the instruments were not part of the usual neurosurgical setup.

One should mention that men in hospital training for consultant posts are to be paid salaries after the internship period that are somewhat higher than those paid by the major teaching hospitals in this country. The financial support at this crucial period in a young man's life permits merit to be a more significant factor in determining selection for advanced training and is a feature of the British system that might well be emulated in this country.

No systematic discussion of salaries to be paid to the various categories of practicing physicians will be attempted here, final decision regarding the salary scales for consultants has not even been made although the profession has been at work since July 5 under the new regime. However, the present salaries of three colleagues and personal friends bear mention. They are consultants with extended complete postgraduate training in a surgical specialty, and they now hold full-time appointments in major hospitals. Each of these men with a family is paid about \$2500 per year after income tax deductions, and this is a representative income for such men under forty years of age throughout England. This permits each a scale of living approximately similar to that which one would obtain in this country on such an income, but the startling fact

type of such requests for special housing, heating, transportation, domestic equipment and so on *ad infinitum*. The building of an additional room on a house, the purchase of more fuel, or more electric heat, the ownership of a car or more gasoline for it—even the buying of a hot water bottle—require governmental permits, or are facilitated by governmental priorities, one avenue to which is a physician's certificate of medical need. Another group of cases in which the doctor acts more as a referee than as a healer is the workmen's compensation group. Although that exists in this country, too, there is a special feature in Great Britain that tends to make the workman dissatisfied since the state and not he himself pays the doctor's bill, he is likely to regard the physician not as his advocate in the dispute but as that of the state from which he is attempting to wrest more money. There is virtually no neutral body of medical men that is employed neither full time nor part time by the state from whom he can secure an opinion unbiased by such employment, so that he may seek the opinions of many doctors, finally utilizing the report of the one who would give him the most. There is still another group, the war veterans, over whose demands for special funds the physicians in Great Britain must act as umpire. The war veteran in this country is entitled to compensation for any medical disability he may develop, only if he is unable to pay for the treatment himself, but the British veteran is so favored only if the disability arose as a direct consequence of his war service. The burden of testifying to this thorny problem falls on the doctor.

Another handicap imposed on the general practitioner is the extreme paucity of special diagnostic facilities at his command. Even routine blood counts are difficult for him to obtain—not to mention quantitative blood chemical analyses and bacteriologic or roentgenographic studies. Almost the only clinicopathological and x-ray departments are those in hospitals, and these are already swamped with work from the hospital itself. The directors of these departments suspect, doubtless rightly, that if the general practitioner were able to call on them at will, many would abuse the privilege, writing out the requests for laboratory work with the same lavish hand that dispenses excuses for absenteeism. The conscientious student of his cases thus has his ardor dampened by the fact that as soon as a patient with an interesting problem appears he must refer that person to a consultant.

The Labour Government announces that it is proposing to set up so-called health centers in which several doctors will have their offices and at which there will be a diagnostic laboratory. No such centers have yet been built, nor are any being projected for the immediate future. It is pertinent to contrast this situation with the type of practice so prevalent in this country for some decades in

which groups of doctors have organized themselves on their own initiative to provide not only laboratory but also roentgenologic studies for their patients, along with specialized consultant services within the group.

The fact that house calls are now free in Great Britain removes one useful restraint from the type of patient who nurses his complaints in silence all day and then decides at midnight that he had better call a doctor. Failure of a physician to answer an emergency call not only may unfairly lose him the patronage of the patient but also is the basis for serious disciplinary action by the General Medical Council or other appropriate agency. One painstaking physician, fearful lest a real emergency be overlooked, has become so exhausted and distraught answering futile night calls that a psychiatrist has had to recommend a protracted period of vacation.

The so-called patient's free care extends to the dispensing of such needed appliances as braces and eyeglasses. He tries in the first instance to get from the general practitioner whatever arch supports or girdles may appear a handy thing to have about. But if the patient is balked at this level the opinion of a consultant may be demanded. In an outpatient clinic in which I was working a man appeared with an excellent result following the removal through a small laminectomy of a midthoracic cord tumor. He put on a little show for us in an effort to get a back brace, making it clear that he thought he was now entitled to this, and meant to have it. A further consequence of the fact that the Government is now the only purchaser of prostheses and braces is the driving out of business of all firms that the Minister of Health does not see fit to support. The doctor may order an appliance for his Health Service patient but he may not designate the firm that is to make it. This proscription is, for example, eliminating from the field one firm that is widely regarded as the best British maker of artificial limbs but is no favorite of the Labour Government.

THE CONSULTANT

And what of the lot of the consultant group? In 1945 a distinguished man in this category told me what striking improvements the reorganization would bring. For the first time the men in training would be paid adequately, and there would be enough of them to relieve the senior staff of onerous duties. The systematic planned utilization of the available personnel for the whole country could only lead to greater efficiency, necessary improvements would have only to be pointed out to the Minister of Health or his representative with direct access to the nation's Treasury and need not depend on the caprice of private gifts as it had before the war. Each major medical school would be the center of a region of the nation with its regional medical board, exercising a salutary continuing influence over the actual medical practice.

selves with medical complaints, a discouraging additional number of them can apparently be counted on to do so. If the task of assessing the ability to lead an active life and the compensability of lack of enthusiasm therefor is to be extended to the entire population, the experience in Great Britain suggests that in this country extended ill feeling between the medical profession and other segments of the nation and a deterioration in the quality of medical care can be anticipated.

I have spent two years as an Oxford medical undergraduate, four years in London and Birmingham during the

war as a practicing surgeon employed by the Ministry of Health for most of this time, and a further recent period of work in England.

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THE EFFECT OF SULFANILAMIDE ON SALT AND WATER EXCRETION IN CONGESTIVE HEART FAILURE*

WILLIAM B. SCHWARTZ, M.D.†

BOSTON

THE importance of the sodium ion in edema is well recognized. If a specific method were available for producing selective inhibition of the renal tubular reabsorption of sodium from the glomerular filtrate, it might well prove useful in the study and treatment of edema. A possible method is suggested by the studies of Pitts and Alexander¹. Under the conditions of their experiments they demonstrated that the renal tubules must make an active addition of acid to the glomerular filtrate to account for the acidity of the urine. The only source of acid large enough to account for the acidification of the urine was considered by them to be hydrogen ions derived from carbonic acid formed in the renal tubular cells. The loss of hydrogen ions by tubular excretion would require the absorption of base from the glomerular filtrate to maintain ionic equilibrium. To test this hypothesis these workers administered sulfanilamide, a specific inhibitor of carbonic anhydrase,² to dogs, presumably inhibiting the formation of carbonic acid in the renal parenchyma. After the administration of sulfanilamide the titratable acidity of the urine fell, and its pH increased. They postulated that reduction in tubular excretion of hydrogen ions had resulted from the inhibition of carbonic acid formation.

It appears that with sulfanilamide administration and decreased acid excretion, the disturbance in acid-base balance should result in failure to reabsorb fixed base from the glomerular filtrate. This loss of fixed base, if maintained, might be expected to lead to diuresis and to the loss of

edema. This paper is a preliminary report of studies that appear to substantiate this hypothesis.

METHODS

Three patients with severe congestive heart failure and fluid retention were selected for study. They were confined to bed and chair during the period of study and fed a constant diet containing about 2000 calories and about 300 mg of sodium. Daily fluid intake was constant. Digitalis was continued, but no ammonium chloride, mercurials or sodium-containing medications were permitted. Urine was collected for twenty-four-hour periods. A saturated solution of thymol in chloroform was employed as a preservative. Blood and urine chemical examinations were carried out in the usual fashion. Analyses of serum and urine for sodium and potassium were made with the Perkin-Elmer flame photometer, model 52A. Sulfanilamide was administered in amounts (4 to 6 gm per day) that were designed to keep the serum level at about 12 mg per 100 cc. The patients were weighed at the same time each day.

CASE REPORTS

CASE 1 The patient was a 48-year-old woman with a history of rheumatic valvular disease for 30 years and progressive cardiac decompensation for 15 years. Digitalis, a low-salt diet, ammonium chloride and semiweekly injections of mercurial diuretics had failed to prevent the accumulation of edema.

Physical examination revealed a thin, markedly dyspneic and orthopneic woman with cardiac enlargement, auricular fibrillation, mitral stenosis and insufficiency and aortic stenosis. There was marked venous distention (venous pressure equivalent to 240 mm of saline solution), fluid at the right lung base, enlargement of the liver to the umbilicus and a ++ pitting edema of the legs. She was continued on digitalis and placed on the constant diet and a fixed daily intake of 2000 cc. After 10 days, during which her weight and sodium output became stable, sulfanilamide was administered for a period of 7 days. The alterations in weight, urine volume and blood and urine constituents are given in Table I.

*From the Medical Clinic, Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School. The expense of this work was defrayed in part by a grant from the Jacob Ziskind Foundation.

†Research fellow in medicine, Harvard Medical School, assistant in medicine, Peter Bent Brigham Hospital, United States Public Health Service Research Fellow.

is the relation of this annual earning to that of other groups in the country. It is indeed a smaller yearly income than that of a skilled mechanic in England working far less "overtime" than these men do. Every one of the skilled laborers in a factory of the father of one of these men has a higher income than he does after his fifteen years of higher education and postgraduate training and experience. The one man of the three who has no familial or other outside source of financial assistance cannot, of course, even afford to own a car. Two of the three men are actively exploring possibilities for leaving the country. One finds it difficult to avoid the impression that the medical profession in England is being burdened beyond the limit of tolerance.

THE PROBLEM

On the basis of the foregoing statements representing a catalogue of facts checked since the writing of this article by four different English physicians now in this country, a personal opinion will be ventured on the significance of these facts to the medical profession in the United States. In the first place, the sorry plight of our British colleagues appears to be due to their having been compelled to accept terms imposed by nonmedical members of the nation. Had they analyzed the defects in their system, presented a well conceived plan for improvements, and then stood fast against ill advised changes, the British people might now be receiving better care and the physicians might be happier about their working milieu. American physicians are or should be more familiar with the shortcomings in the present scheme here than anyone else. Unless they come up with a constructive program correcting these faults—perhaps even if they do—they can expect outside imposition of laws that, the British experience suggests, will at least in some aspects be detrimental to the best interests of the patient and his doctor.

The purpose of this article will be grossly misconstrued if it is considered an argument against any change in the present organization. The thesis is, on the contrary, that changes must occur and that the problem should be analyzed and the most logical type of reorganization effected.

One crucial feature of the difficulty in England, I believe, is that the responsibility for being healthy and economically self-sufficient has been shifted from the patient to his physician. I wish that the medical profession knew enough about human personality in health and disease to shoulder this responsibility, but I am convinced that I at least do not. When the political order in a country offers a helping hand to its ill citizens to assist them to struggle to their economic feet, the main burden of recovery should still fall on the patient. All physicians have seen striking examples of protracted convalescences that were being paid for by someone else, in contrast with brisk returns to activity in

patients with the same disorder who were determined to lead active lives again at the earliest moment.

There are three groups of cases in which the physician is at a peculiar disadvantage when the patient sheds the responsibility for getting well. In the first of these the person with a purely psychologic or simulated disorder is thought to have organic disease. In a manuscript currently in preparation I am including the case of a nurse who described in herself the symptoms of trigeminal neuralgia sufficiently graphically so that in five different major teaching hospitals she had a total of three alcohol injections and two operations on the trigeminal pathways, and yet after scores of hours of study by several examiners her physicians are still uncertain whether she ever had trigeminal neuralgia. This represents one of many organic disorders—for example, migraine, angina pectoris and other neuralgias—in which no objective signs of abnormality are necessarily present, and by virtue of which the patient without the disorder may consciously or unconsciously delude the physician with a convincing description.

The converse situation, in which an organic disorder is diagnosed as psychoneurosis by the physician, is also seen with disconcerting frequency. During the war I eventually saw several men whose presenting symptoms of their intracranial tumors were much more suggestive to their original medical officers of an inordinate desire to avoid combat than of any organic disease. One of the most unattractive features of medical practice in the armed forces is the frequent necessity of distinguishing the sick from those who complain of illness to avoid duty. The inefficient means for grappling with this problem is one of the causes for such a disproportionately large need for medical officers in the armed forces.

But the most difficult group of all is the much larger one of the patients with unequivocal evidence of structural malady in whom the question arises whether the complaints are excessive for the degree of anatomic damage present. How can the doctor, who unfortunately cannot feel the patient's pain, tell whether the headache that allegedly persists after a fracture of the skull or a back that goes on aching after a protruded intervertebral disk is removed should be treated by a prompt return to work or some financially compensable and less arduous tactic? I fear that even after hours of patient effort one emerges only with a guess.

In the present state of ignorance, if the doctor is to keep the good will of the community and his own self respect, he must do his best to see that his duties are so delineated, and the society so organized, that the number of cases in the foregoing three categories will be kept to a minimum. As soon as the political order or any other environmental feature makes it advantageous for any citizens to present them-

The effect on urinary sodium and potassium is shown in Figure 1. On the 3rd day of treatment the patient became slightly confused. This continued until 48 hours after the drug was discontinued, at which time she showed complete clearing of her sensorium. At no time was the confusion of sufficient severity to interfere with adequate co-operation. At the end of therapy the venous pressure had fallen to 170 mm of saline solution. The liver receded 6 cm, edema disappeared, and the amount of fluid in the chest diminished. The patient was no longer orthopneic and exertional dyspnea was decreased.

CASE 2 The patient was a 54-year-old woman with a history of rheumatic heart disease since the age of 12. Four years before admission she had suffered a severe episode of substernal pain followed by the onset of heart failure. Since that time she had grown progressively weaker and more dyspneic and had developed ascites. Treatment had consisted of digitalis, a low-salt diet and mercurial diuretics. Physical examination revealed a cachectic, dyspneic woman with marked cardiac enlargement, auricular fibril-

below the right costal margin, and there was +++ edema of both legs. The patient was continued on digitalis, placed on the constant diet and given a fixed 2000-cc. fluid intake. After 6 days, during which his weight and sodium output became stable, sulfanilamide was administered. This was well tolerated for 8 days, and during this time the dyspnea and

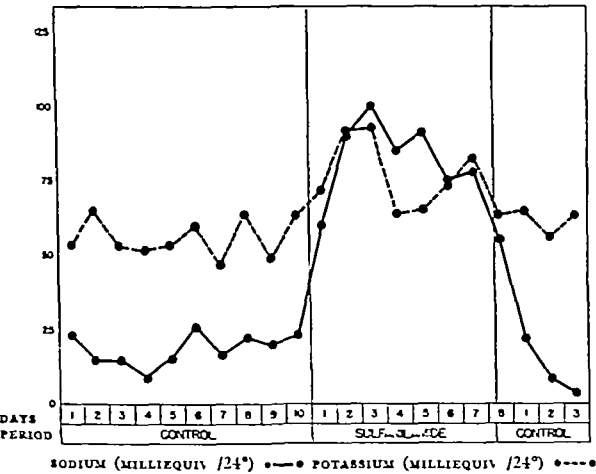


FIGURE 1 Effect of Sulfanilamide on Urinary Sodium and Potassium in Case 1

lation and mitral insufficiency and stenosis. Rales were present at both lung bases. The liver edge extended 6 cm below the right costal margin. There was no peripheral edema. During the first 16 days the patient was treated with a low-salt diet, digitalis, ammonium chloride and six 2-cc injections of mercury. This was accompanied by a weight loss of about 2 kg. The sixth injection of mercury was given on the 16th hospital day, and in the next 24 hours she gained 0.5 kg. She was then placed on the constant diet, and fluid intake was fixed at 1600 cc per day. After 4 days, during which her weight and sodium output became constant, sulfanilamide was administered. After 48 hours the drug was discontinued because of nausea, malaise and methemoglobinemia. During this period there was no appreciable change in physical findings. Changes in weight, urine volume, and blood and urine constituents are shown in Table 2, and the effect on urinary sodium and potassium in Figure 2.

CASE 3 A 64-year-old man gave a history of progressive heart failure of 3 years' duration. He had been known to have hypertension and coronary-artery disease for 8 years. Despite treatment with digitalis, salt restriction, ammonium chloride and mercurial diuretics twice a week he had become markedly dyspneic, orthopneic and edematous. Physical examination revealed a dyspneic, orthopneic man with auricular fibrillation, fluid at the left-lung base and rales at the right-lung base. The liver edge was 8 cm

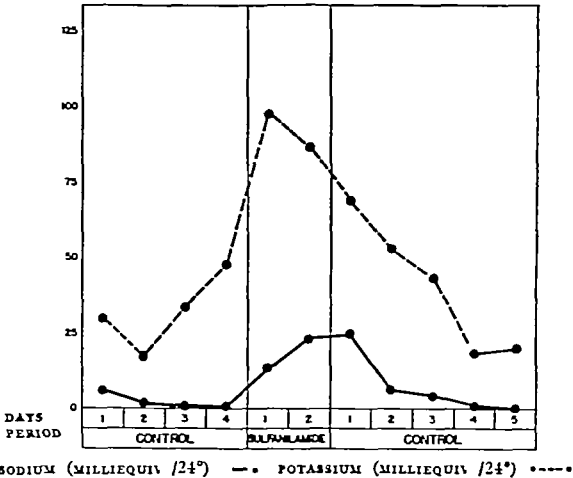


FIGURE 2 Effect of Sulfanilamide on Urinary Sodium and Potassium in Case 2

orthopnea improved markedly and the leg edema diminished to +. The liver decreased in size, and the venous pressure fell from 230 mm to 100 mm of saline solution. Changes in weight, urine volume, and blood and urine constituents are shown in Table 3, and the effect on urinary sodium and potassium in Figure 3. On the 7th day of treatment

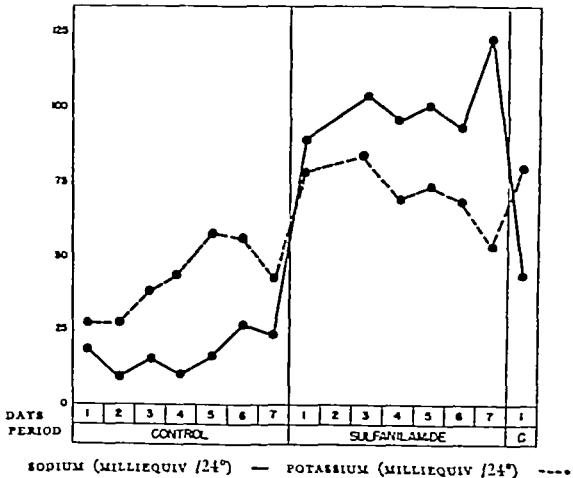


FIGURE 3 Effect of Sulfanilamide on Urinary Sodium and Potassium in Case 3

the patient had a shaking chill and developed a temperature of 105°F. Sulfanilamide was discontinued, and penicillin and streptomycin begun after blood cultures had been taken. During the next 4 days the patient continued to show a spiking fever, with temperature elevations as high as 105°F and remissions to virtually normal temperatures. On the 5th day the temperature returned to normal, and the patient's

TABLE 1 Changes in Weight, Urine Volume and Blood and Urine Constituents in Case 1

DAYS	BODY WEIGHT kg	INTAKE cc	URINE VOLUME cc	SERUM CHLORIDE milliequ/liter	SERUM SODIUM milliequ/liter	SERUM POTASSIUM milliequ/liter	URINE CHLORIDE milliequ/24 hr	URINE SODIUM milliequ/24 hr	URINE POTASSIUM milliequ/24 hr	CARBON DIOXIDE millimol/liter	METHEMOGLOBIN gm per 100 cc	SULFINILAMIDE mg per 100 cc
Control												
1	53.6	2000	2000	—	145	—	24.0	24.0	54.0	28.5	0.72	—
2	52.2	2000	2010	—	—	—	20.1	15.1	65.5	—	—	—
3	53.0	2000	1250	—	—	—	16.2	15.6	53.1	—	—	—
4	53.4	2000	1335	—	—	—	21.3	9.6	51.9	25.3	0.27	—
5	53.0	2000	1650	106	144	—	26.4	15.3	53.6	—	—	—
6	53.2	2000	1810	106	—	4.8	32.5	26.1	60.1	27.9	0.18	—
7	53.0	2000	1510	—	—	—	22.6	16.9	46.8	—	—	—
8	53.0	2000	2015	108	144	4.8	40.3	22.8	64.0	25.0	—	—
9	53.0	2000	1370	—	—	—	27.4	20.0	49.3	—	—	—
10	52.8	2000	1900	—	—	—	38.0	23.4	63.8	—	—	—
Sulfanilamide												
1	52.8	2000	1840	109	144	5.0	27.6	60.5	71.7	25.2	0.27	—
2	52.0	2000	2280	110	144	—	43.3	90.0	91.2	22.7	0.18	6.0
3	52.0	2000	2500	110	143	5.0	65.0	100.0	92.5	21.2	0.26	12.0
4	51.1	1400	1920	113	145	—	65.2	84.7	64.3	—	0.18	13.0
5	50.8	2000	1620+	118	144	—	78.2+	91.0+	65.5+	20.0	0.36	12.0
6	50.2	2000	1840	113	—	—	99.1	75.4	73.6	18.6	—	11.0
7	49.6	2000	2080+	—	—	—	70.7+	76.0+	82.2+	—	—	—
8	49.0	2000	1815	112	147	5.1	61.8	55.6*	63.5	19.3	0.27	13.0†
Control												
1	48.2	2000	1660	114	146	—	64.7	21.6	64.7	20.2	—	6.0
2	48.2	2000	1440	114	145	—	46.8	8.6	56.1	20.7	—	2.0
3	48.6	2000	1720	111	—	—	49.0	3.7	63.2	21.5	—	1.5

*Sodium excretion during the twenty-four hours following final dose of sulfanilamide

†Sulfanilamide level immediately before drug was discontinued

TABLE 2 Changes in Weight, Urine Volume and Blood and Urine Constituents in Case 2

DAYS	BODY WEIGHT kg	INTAKE cc	URINE VOLUME cc	SERUM CHLORIDE milliequ/liter	SERUM SODIUM milliequ/liter	SERUM POTASSIUM milliequ/liter	URINE CHLORIDE milliequ/24 hr	URINE SODIUM milliequ/24 hr	URINE POTASSIUM milliequ/24 hr	CARBON DIOXIDE millimol/liter	METHEMOGLOBIN gm per 100 cc	SULFINILAMIDE mg per 100 cc
Control												
1	38.4	1875	1120	—	—	—	29.6	6.0	17.2	—	—	—
2	38.3	1600	1120	92.4	140	—	5.4	1.7	33.9	33.4	—	—
3	38.0	1600	1300	—	—	—	4.8	0.8	47.2	—	—	—
4	38.5	1600	1250	—	—	4.0	4.0	0.8	—	—	—	—
Sulfanilamide												
1	38.9	1600	1380	92.5	137	—	2.6	13.8	97.9	33.3	—	—
2	38.8	1600	1760	95.2	—	—	4.1	23.1	86.2	30.2	1.1	9.2
Control												
1	38.5	1600	1050	98.3	140	4.2	4.0	26.2	68.0	26.2	2.05	14.0
2	38.4	1600	965	103.0	—	—	9.1	6.1	52.8	26.6	1.21	8.5
3	38.8	1600	830	104.0	—	—	3.9	4.1	43.0	—	0.45	3.0
4	38.8	1600	600	—	—	—	3.5	0.6	18.0	—	—	—
5	39.2	1600	485	—	—	—	3.5	0.1	20.9	—	—	—

Sulfanilamide is unquestionably too toxic a drug for prolonged or routine use in the inhibition of carbonic anhydrase. It should be noted that whereas the amino group in the para position to the sulfonamide group is necessary for the antibacterial activity of sulfanilamide,²⁻⁸ it is not essential for the effect on carbonic anhydrase. It is the free sulfonamide group that is directly concerned with the inhibition of this enzyme.² A number of other sulfonamides with free sulfonamide groups have been shown to have an effect on carbonic anhydrase similar to that of sulfanilamide.²⁻⁹ In addition, Höber¹⁰ has demonstrated that the addition of sulfanilamide and of compounds with an unsubstituted sulfonamide group to the perfusion fluid of an isolated frog kidney changes the reaction of the secretion from acid to alkaline. Compounds of this type are under investigation in an attempt to find one less toxic than sulfanilamide. The evidence available at present does not permit a conclusion about the potential relative merits of this method of diuresis as compared to others now in common use. Studies also have been too short to indicate whether the increased base excretion would continue if carbonic anhydrase inhibition were maintained for a prolonged period in an edematous patient.

SUMMARY

Evidence indicating that sulfanilamide is capable of producing an increased sodium, potassium and water excretion in patients with congestive heart failure is presented. It appears that the inhibition of carbonic anhydrase in the cells of the renal tubules is responsible for this phenomenon. Other sulfonamides that are also inhibitors of carbonic anhydrase are under investigation in an effort to find a compound less toxic than sulfanilamide.

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TABLE 3 Changes in Weight, Urine Volume and Blood and Urine Constituents in Case 3

DAYS	Body Weight kg	INTAKE cc	URINE VOLUME cc	SERUM CHLORIDE milliequiv/liter	SERUM SODIUM milliequiv/liter	SERUM POTASSIUM milliequiv/liter	URINE CHLORIDE milliequiv/24 hr	URINE SODIUM milliequiv/24 hr	URINE POTASSIUM milliequiv/24 hr	CARBON DIOXIDE millimol/liter	METHILMO GLOBIN gm per 100 cc	SULFANIL- AMIDE mg per 100 cc
Control												
1	61.6	1120	595	110	—	—	27.2	18.5	27.4	27.2	—	—
2	62.0	1350	475	109	—	—	14.4	19.1	27.0	—	—	—
3	63.2	2000	935	—	—	—	27.6	14.8	38.2	—	—	—
4	62.6	2000	1170	—	—	—	31.8	10.6	43.4	—	—	—
5	62.2	2000	2015	106	—	—	33.6	16.0	57.0	28.8	—	—
6	62.6	2000	1735	110	142	—	40.9	26.4	56.2	29.2	—	—
7	62.4	2000	1420	110	—	—	25.1	23.5	42.6	—	—	—
Sulfanilamide												
1	62.3	2000	1805	—	—	5.0	40.8	88.2	78.6	25.8	0.35	5.5
2	61.8	2000	1730	110	—	—	51.0	103.6	83.0	23.8	0.63	8.5
3	61.0	2000	2030	112	146	4.4	63.8	95.4	69.0	—	—	—
4	60.2	2000	1940	—	—	4.2	78.1	100.1	73.7	22.1	0.45	12.0
5	59.2	2000	1510	114	—	—	81.6	92.1	68.0	19.6	0.45	8.0
6	59.2	2000	1135	115	144	4.5	100.4	123.1	53.7	19.8	0.45	11.0
7	58.4	2000	—	—	—	—	—	—	—	—	—	—
Control	58.2	2000	1120	117	—	—	60.5	43.7	79.1	17.6	0.63	8.5

*Specimen lost.

further course was uneventful. During this period there were no signs of increasing heart failure. No cause for the fever was ascertained. There was no evidence of blood stream, urinary-tract or other infection. Whether the fever represented a reaction to sulfanilamide is a matter of conjecture.

DISCUSSION

All patients showed an increase in sodium and potassium excretion within the first twenty-four hours of sulfanilamide administration. The 2 patients in whom it was possible to continue the drug for a seven-day period maintained a high daily output of sodium in the urine, which was four to five times the control value, and exhibited a weight loss that correlated with the increase in sodium output. The urine pH increased in all cases. At the same time there was a sharp fall in carbon dioxide combining power of the serum accompanied by an increase in chloride. These changes can best be explained by an inhibition of carbonic anhydrase in the renal parenchyma with retention of hydrogen ions and concomitant diminution of sodium reabsorption. It was of some interest that the withdrawal of sulfanilamide resulted in a fall in sodium excretion to lower levels than those observed in the pretreatment period ("rebound phenomenon") in the 2 patients observed for a prolonged period.

The inhibition of carbonic anhydrase by sulfonamides was described by Mann and Keilin² in 1940. They demonstrated that only compounds with a free sulfonamide group are inhibitors of carbonic anhydrase. It would not be expected, therefore, that any of the recent sulfonamide compounds that have replaced sulfanilamide in clinical use would be capable of inhibiting carbonic anhydrase since they contain substituted sulfonamide groups.

Studies on acid-base balance in patients receiving sulfanilamide,³⁻⁶ when this drug was the only compound in general clinical use, revealed a pattern that might have been predicted had its action on carbonic anhydrase been known. Subjects were found to show an increase in urine volume and sodium excretion accompanied by an increase in the pH of the urine. At the same time there was a reduction in serum carbon dioxide combining power and pH. Roughton and his co-workers⁷ studied a group of patients receiving 2 to 3 gm of sulfanilamide daily. They found that during rest and moderate exercise (five or six times resting metabolism) the rate of carbon dioxide elimination was not impaired.

There was no response to appropriate treatment instituted on a tentative diagnosis of rheumatic heart disease and mitral stenosis and insufficiency, and death occurred on the 25th hospital day. Before death the face and hands became edematous, and the color of the skin was almost heliotrope. The hemoglobin and red-cell count fell to half the normal values. Anuria developed 48 hours before death, and the urine contained red cells and a few casts. During the last 5 days of life the temperature was elevated to 101°F. The final clinical diagnosis was rheumatic heart disease, mitral stenosis and insufficiency, bacterial endocarditis, cardiac hypertrophy, myocardial fibrosis and terminal nephritis.

At autopsy* the heart weighed 500 gm. The right ventricle, right auricle and pulmonary artery were greatly dilated. The myocardium was flabby. The orifice of the mitral valve was narrowed to a mere slit, and the margins were distorted by soft, friable vegetations (Fig. 3). These vegetations extended along the free surface of the valve to the chordae tendineae, which were thickened and shortened. The foramen ovale, which measured 5 cm in diameter, was not involved. The coronary vessels were patent. The mitral valve measured 10 cm, the aortic valve 7.1 cm, the tricuspid valve 16.0 cm, and the pulmonary valve 9.5 cm. The left ventricle was 11 cm thick. The right ventricle was 0.5 cm thick, and its diameter was 11.5 cm. The pathologist's anatomic and microscopical diagnoses were interauricular septal defect, subacute bacterial endocarditis, healed rheumatic endocarditis, cardiac hypertrophy and dilatation, multiple pulmonary infarcts and focal embolic nephritis.

DISCUSSION

To date the combination of interauricular septal defect and mitral stenosis (Lutembacher's syndrome) seems to have been recorded in combination with bacterial endocarditis in only 3 cases.¹⁻³ The complete report of Geiger and Anderson,³ who made the diagnosis before death in a patient observed for eleven years, makes any extended comment on the case reported in this communication entirely superfluous.

The lesson of the case is obviously the overlooked diagnosis. It was a diagnostic as well as a therapeutic error to eliminate subacute bacterial endocarditis from consideration on the basis of a single negative blood culture; antibiotic therapy should have been instituted on the mere suspicion. The diagnosis of interauricular septal defect was overlooked for the most usual of all reasons—failure to recollect an uncommon though by no means rare condition. Actually, the roentgenologic and fluoroscopic diagnostic criteria were met,^{3,4} the electrocardiogram was characteristic, and the cardiac findings and ante-mortem lividity (*cyanose tardive*) were also characteristic. Had these observations been evaluated properly and in their entirety, there is every reason to believe that a correct diagnosis could have been made before death.

Another point of interest in this case is the remarkable tolerance shown by the patient to the

difficulties of life. Such tolerance is frequent in patients with congenital interauricular septal defects.⁵

SUMMARY

A case is recorded of interauricular septal defect combined with mitral stenosis (Lutembacher's syndrome) and with bacterial endocarditis. It is



FIGURE 3 Interauricular Septal Defect Associated with Mitral Stenosis and Subacute Bacterial Endocarditis. Note the vegetations extending proximally from the free border of the mitral valve.

apparently the fourth case of this kind to be put on record. Diagnostic considerations are briefly discussed.

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*Performed by Dr. R. E. Miller, Department of Pathology, Dartmouth Medical School.

LUTEMBACHER'S SYNDROME ASSOCIATED WITH SUBACUTE BACTERIAL ENDOCARDITIS*

Report of a Case

EDWARD R. H. KURZ, M.D.,† AND ISIDORE FISCHER, M.D.‡

WHITE RIVER JUNCTION, VERMONT, AND NEW YORK CITY

THE following case of Lutembacher's syndrome (interauricular septal defect and mitral stenosis) associated with subacute bacterial endocarditis is considered worthy of comment since it appears to be the fourth such case to be recorded in the medical literature.

A forty-seven-year-old man was admitted to the hospital after he had suffered for 2 months from progressively more

Positive cardiac findings included a systolic thrill at the apex, a very short diastolic murmur at the mitral area, a harsh, blowing diastolic murmur in the second and third left interspaces to the left of the sternum, and a loud systolic apical murmur transmitted to the axilla. The fluoroscopic findings consisted of moderate enlargement of the outflow and inflow tracts of the left ventricle, characterized by elongation, horizontal and vertical enlargement of the left auricle, marked enlargement of the outflow tract of the right ventricle, with some enlargement of the inflow tract, marked enlargement in the region of the pulmonary conus, and enlargement of the appendicular portion of the right auricle.

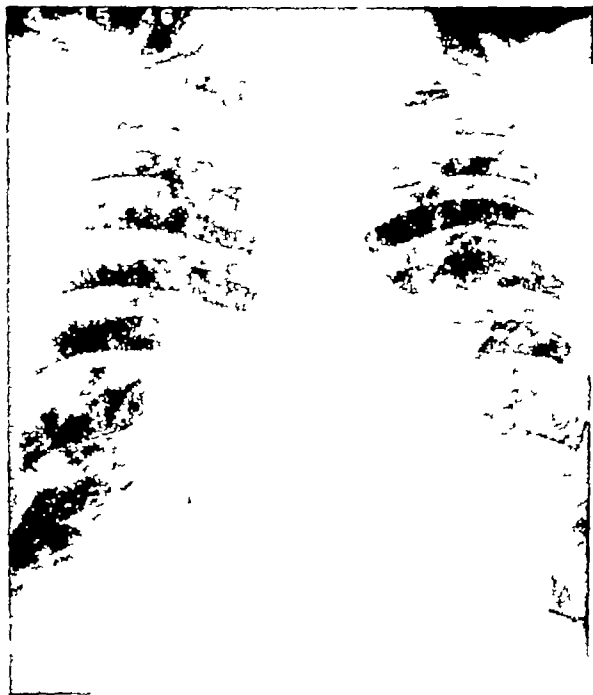


FIGURE 1 Roentgenogram of Chest, Showing Enlarged, Triangular Cardiac Shadow, Prominent Pulmonary Conus, Thickened, Hazy Pulmonary Shadows and Prominent Hilar Shadows

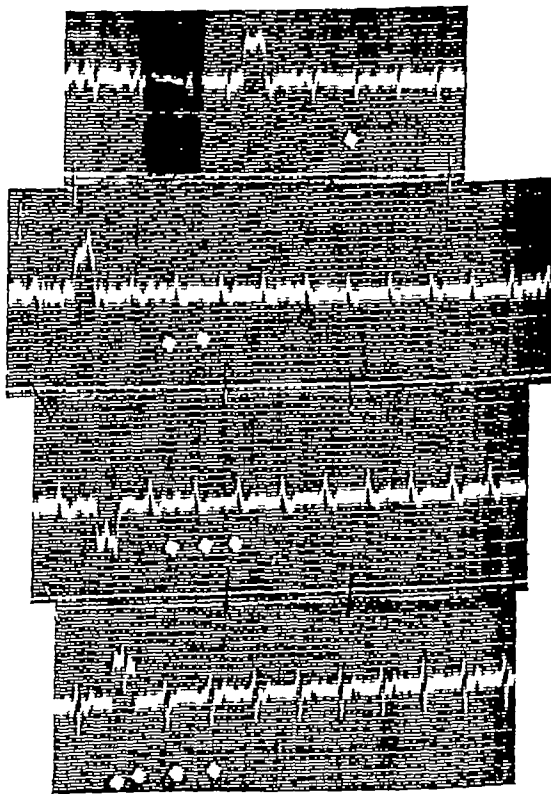


FIGURE 2 Electrocardiogram, Showing Auricular Fibrillation, Marked Right-Axis Deviation, Low-Voltage T Waves and Slurred and Notched QRS Complexes

severe dyspnea, orthopnea and hemoptysis. The past history was entirely irrelevant except for an attack of apparent rheumatic fever 20 years earlier. In the interim he had been in active service in the Royal Canadian Field Artillery and had done work in a woolen mill.

*From the Veterans Administration Hospital White River Junction Vermont.

†Chief of medicine Veterans Administration Hospital White River Junction Vermont.

‡Assistant adjunct physician, Department of Internal Medicine Bronx Hospital formerly medical officer (ward) Veterans Administration Hospital White River Junction Vermont.

The arch of the aorta appeared normal. A roentgenogram of the chest (Fig. 1) showed cardiac enlargement, prominence of the pulmonary conus, thickened pulmonary shadows and prominent hilar shadows. The chief electrocardiographic finding (Fig. 2) was marked right-axis deviation. Laboratory examinations were within normal range, and a blood culture was sterile.

With few exceptions clinical efficacy can be predicted from antibacterial potency. Table 1 shows the generally accepted clinical indications for each drug, these parallel, on the whole, the growth-inhibiting capacities of the drugs for each species in vitro. There are a few outstanding exceptions, however, which are still unexplained. Clinical *diphtheria* does not respond to treatment with penicillin although levels can be established that are more than adequate for control of the bacillus in vitro. Penicillin as an adjunct to antitoxin and other measures is nevertheless indicated for the prevention of suppurative complications, and the carrier state responds dramatically to the drug.³²⁶ *Typhoid and paratyphoid fevers* are refractory to streptomycin therapy despite sensitivity of the organisms.²⁹³ *Brucellosis* also fails to respond to streptomycin.³²⁷ *328*, recent reports, however, point to a synergism of sulfadiazine and streptomycin,³²⁹ and a small number of acute and chronic cases in human beings have been cured by the combined drugs.³³⁰ *331*

It will be observed that the affinities of penicillin and streptomycin do not overlap but that sulfonamides share with either drug their potency against a number of species. When sulfonamides and penicillin are equally effective, the latter is the drug of choice for reasons of comparative toxicity. In meningococcal meningitis penicillin is looked upon with disfavor because of its poor penetration into the normal cerebrospinal fluid, most clinicians favor sulfadiazine,²⁹¹ or sulfadiazine in addition to penicillin. Opinion is divided on the treatment of pneumococcal pneumonia, both drugs are highly effective and in general use. When sulfonamides and streptomycin are equally effective the former are often favored because they are less toxic. Of the many diseases once treated with sulfonamides³³² *333* only cholera, chancroid, lymphogranuloma inguinale and trachoma remain uniquely responsive to these drugs, and uninfluenced by either penicillin or streptomycin. Closely related to the sulfonamides are the sulfone drugs, — diasones, promine and promizole, — which are being used with encouraging success in the treatment of leprosy,³³⁴ and other sulfones have a promising tuberculostatic action.³³⁵ *337* Several general reviews of sulfonamides in clinical practice have appeared.¹⁹⁶ *333* *339*

Penicillin Therapy

The remarkable successes achieved with penicillin in streptococcal and staphylococcal infections, especially in subacute bacterial endocarditis,³⁴⁰ in the prophylaxis of streptococcal infection,¹⁸³ in gonorrhea,³⁴¹ *342* in pneumococcal infection, in gas gangrene, in actinomycosis³⁴³ and in a variety of

surgical conditions³⁴⁴ are fully presented by many clinical investigators.

Perhaps the most remarkable consequence of the penicillin era has been the complete revolution brought about in antisyphilitic therapy. Cure rates in primary and secondary syphilis compare favorably with those obtained by the best of the older methods and without the previously attendant risk of grave injury from the therapeutic agent.³⁴⁵ *345* Evaluation of results in treatment of tertiary syphilis requires many years of follow-up study, but it is not unlikely that this outcome will also be favorable.³⁴⁶ The drug is certainly beneficial in cerebrospinal forms of the disease,³⁴⁷ *348* but there is still doubt whether it is as effective as arsenical and fever therapy. Various combined treatments have been advocated, directed especially toward the 5 to 10 per cent of cases that are resistant to repeated courses of penicillin. Thus, oxophenarsine and fever have been used as adjuncts to penicillin, but sufficient data are not yet available for sound evaluation. The work of Moore³⁴⁵ and Pillsbury,³⁴⁹ the authoritative reports of the Syphilis Study Section of the National Research Council³⁵⁰ *351* and the recent review by Crawford³⁵² present full details of the efficacy of penicillin in syphilis. Several other more general summaries of the clinical uses of penicillin have appeared.²²³ *339* *353*–*357*

Streptomycin Therapy

With the exceptions noted above, streptomycin is effective in the clinical treatment of diseases produced by gram-negative bacteria. It has proved dramatically successful in tularemia³⁵³ *359* (particularly the pneumonic form) and in plague.³⁶⁰ It is strikingly curative also in meningitis due to *Haemophilus influenzae*,¹⁷⁹ *361* *362* in infection due to *Klebsiella pneumoniae* (Friedländer's bacillus) and in meningitis due to salmonella organisms, despite its inefficacy in enteritis caused by *Salmonella enteritidis*. It has proved useful in the control of dysentery of the *Shigella dysenteriae* form, in relapsing fever due to *Borrelia recurrentis* and in granuloma inguinale,³⁶³ *364* in which it appears to be far superior to the organic antimonials. Its main surgical uses have been in the preoperative sterilization of the bowel³⁶⁵ and in a variety of local infections caused by gram-negative bacilli.³⁶⁶ Its most widespread employment has probably been in the treatment of chronic urinary-tract infections due to *Proteus vulgaris*, *Aerobacter aerogenes* and *Pseudomonas aeruginosa* and other gram-negative species, here results have been good, but relapse is common, resistance develops frequently, and streptomycin cannot replace surgery when an anatomic abnormality is at the root of the infectious process.²²⁵ *367*

Full discussion of the advances made in the therapy of tuberculosis with streptomycin is beyond the scope of this review. In brief, the drug has a

*Adoption of the revised nomenclature " Hansen's disease" is advocated by the patients at the Carville Leprosarium.³⁵¹

MEDICAL PROGRESS

ANTIBACTERIAL CHEMOTHERAPY* (Concluded)

AVRAM GOLDSTEIN, M D †

BOSTON

Binding to Plasma Protein

The experiments of Davis³⁰⁷⁻³¹⁰ and subsequent reports by the same author and others³¹¹⁻³¹² established that sulfonamide action depends upon the level of *unbound* drug in the plasma water. At therapeutic concentrations sulfanilamide is protein bound to an extent of 20 per cent, sulfapyridine 40 per cent, sulfathiazole 75 per cent, sulfadiazine 56 per cent, sulfamerazine 84 per cent, and sulfamethazine 84 per cent.^{289, 303, 313, 314} It should be noted, however, that the usual technics for determining plasma levels do not distinguish between bound and unbound drug. The accepted bacteriostatic thresholds for various organisms also refer to total (bound and unbound) sulfonamide. Consequently for clinical purposes no distinction need be made, the total plasma sulfonamide level is a correct guide to the efficacy of treatment.

On the other hand the binding of penicillins by plasma protein presents some practical problems. This binding increases progressively in the order $X < G < \text{dihydro-F} < K$,^{315, 316} following the generally established principle^{317, 318} that interaction with protein is positively correlated with the length of alkyl side-chains. Biologic assay methods may be distorted by a high degree of binding, thus, the dilution of plasma containing penicillin K results in a reversible dissociation, more unbound penicillin becoming available in the assay than was present in the original plasma. Proper corrections should be made for such effects.³¹⁹

It has been established that the usual order of potency *in vitro* is $K > X > G > F$, whereas *in vivo* the order becomes $X > G > F > K$.³²⁰ The strikingly decreased effectiveness of penicillin K *in vivo* has been attributed to its very appreciable binding to plasma protein (86 to 95 per cent).^{315, 319} It is likely that other factors are also involved since penicillin K is not recovered quantitatively from the urine,³⁸⁸ is apparently destroyed in the plasma^{321, 322} and is inactivated by kidney and liver slices more rapidly than the other penicillins.³²³ On the other hand penicillin X, which is almost as highly bound as G, gives higher and more prolonged blood levels than the latter,³²⁴ and has proved more effective, weight for weight, than any of the other penicillins in the cure of a number of infections.³²⁰

The binding of streptomycin to plasma protein, according to one report,³²⁵ is negligible at therapeutic concentrations.

Most chemotherapeutics are bound reversibly, chiefly to the albumin fraction of the plasma. The relation between the extent of binding and antibacterial potency or toxicity to host tissues is by no means obvious. In the sulfonamide series, sulfadiazine and sulfathiazole, which are bound to the greatest extent, are also the most effective antibacterial agents. In the penicillin series the most highly bound compound is also the least effective *in vivo*. There appears to be no correlation here between affinity for plasma protein and toxicity.

One might surmise, especially from the penicillin findings, that binding to plasma protein is an undesirable feature in a chemotherapeutic. This should not be true, however, unless the concentration of *unbound* drug is thereby reduced below the required level. Theoretically, the protein-drug system is a buffer. At constant protein concentration the *fraction* of a total drug that is bound will be higher at low drug levels and lower at high drug levels. The *amount* of bound drug, however, will increase as the drug level is raised. As a consequence, an appreciable quantity of drug may be held in protein combination, to be released progressively as the drug level falls, the bound drug meanwhile being protected from rapid renal excretion. In this view protein-bound drug would act as a reversible depot, tending to damp abrupt rises and falls of the plasma level curve. Whether such a highly desirable effect will actually occur or whether undesirable reduction of potency (penicillin K) will result must depend upon the specific characteristics (dissociation constant and so forth) of each chemotherapeutic. The practical effects of protein binding upon the dynamic aspects of drug action have not been investigated sufficiently for generalizations to be made. Certain aspects of the problem are discussed by Davis⁶ in a recent review.

CLINICAL APPLICATIONS

The practical value of a chemotherapeutic is determined by many factors, the most important of which are the sensitivity of the pathogenic organisms, the ease of maintaining effective drug levels, the toxicity of the drug and the natural course of the disease.

*From the Department of Pharmacology, Harvard Medical School.
†Associate in pharmacology, Harvard Medical School.

this may occasionally prove disastrous is indicated by a report of bacteremia due to *Esch col* with a preponderant throat culture of the same organism in a penicillin-treated patient,³⁵¹ a case of bacteremia caused by *H influenzae* under similar circumstances,³⁵² bacteremia (*Staphylococcus aureus*) in a patient receiving streptomycin,^{362 352} peritonitis due to a streptomycin-resistant strain of *A aerogenes* in another patient treated with streptomycin³⁶⁵ and similar occurrences.^{352 353} As the problem has not assumed alarming proportions, one must assume that when a specific chemotherapeutic

antibacterial affinities, and others with spectrums that overlap those of the older drugs. New affinities obviously open the way to control of the few bacterial infections still eluding specific therapy. The most important of these are the typhoid infections, tuberculosis, the fungal diseases, diphtheria, brucellosis and, in a different group, the rickettsial and virus diseases. Of equal importance would be the availability of more than a single agent with which to attack a given pathogen. Thus, one could prevent the development of resistance by combined attack, combat resistant organisms once established

TABLE 1 (Continued)

INFECTIVE ORGANISM	PRINCIPAL DISEASE	SULFONAMIDES	PENICILLIN	STREPTOMYCIN	OTHER AGENTS
<i>Malloomyces mallei</i> (<i>Bacillus mallei</i>)	Glanders	Not effective	Not effective	Effective	
<i>Haemophilus influenzae</i>	Meningitis	Partially effective	Not effective	Drug of choice	Polymyxin (insufficient evidence)
<i>Haemophilus pertussis</i>	Pertussis	Not effective	Not effective	Partially effective	Polymyxin (insufficient evidence)
<i>Haemophilus ducreyi</i>	Chancroid	Drug of choice	Not effective	Effective	
<i>Klebsiella pneumoniae</i>	Friedländer pneumonia	Partially effective	Not effective	Drug of choice	Polymyxin (insufficient evidence)
<i>Klebsiella granulomatis</i>	Granuloma inguinale	Possibly effective (insufficient data)	Not effective	Drug of choice	
<i>Mycobacterium tuberculosis</i>	Tuberculosis	Not effective	Not effective	Effective for some forms	PAS or sulfones with streptomycin
<i>Mycobacterium leprae</i>	Leprosy (Hansen's disease)	Not effective	Not effective	Partially effective	Sulfones
<i>Treponema pallidum</i>	Syphilis	Not effective	Drug of choice	Not effective	Bacitracin (insufficient evidence)
<i>Treponema pertenae</i>	Yaws	Not effective	Drug of choice	Not effective	
<i>Leptospira</i> species	Weil's disease	Not effective	Drug of choice	Partially effective	
<i>Borrelia</i> species	Vincent's angina	Not effective	Drug of choice	Partially effective	
<i>Spirillum minus</i>	Rat-bite fever	Not effective	Drug of choice	(Insufficient evidence)	
<i>Actinomyces</i> species	Actinomycosis	Effective	Drug of choice	Not effective	
Other pathogenic fungi	Various infections	Not effective	Not effective	Not effective	
Rickettsiae species	Typhus and related fevers	Possibly effective (insufficient evidence)	Possibly effective (insufficient evidence)	Possibly effective (insufficient evidence)	Chloromycetin and aureomycin PABA (insufficient evidence)
Viruses	Lymphogranuloma inguinale	Drug of choice	Partially effective	Insufficient evidence	Aureomycin
	Ornithosis and psittacosis	Possibly effective (insufficient evidence)	Probably effective	Insufficient evidence	
	Trachoma	Drug of choice	Not effective	Insufficient evidence	
	Other virus diseases	Not effective	Not effective	Not effective	
All diseases of unknown etiology		Not effective	Not effective	Not effective	

*Occasionally useful in infections due to organisms resistant to sulfonamides or penicillin or both

†Useful only for carrier state or to prevent suppurative complications (does not cure)

‡But drug of choice in meningitis caused by this organism

eradicates certain organisms and allows others to flourish unchecked, the body defenses are usually capable of holding the latter within bounds. The interesting question raised by this curious phenomenon is whether the present chemotherapy is too specific or not specific enough. Would it be preferable to select for elimination a single pathogenic species, or should the chemotherapeutic produce a general reduction of all bacterial forms?

NEW CHEMOTHERAPEUTICS

An increasing number of new chemotherapeutics are becoming available, some with entirely original

or replace a chemotherapeutic to which the patient had become sensitive. Less toxic substitutes for streptomycin would prove especially useful. These, in addition to the usual criteria, are proposed as standards for evaluating new chemotherapeutics.

Para-aminosalicylic Acid (PAS)

In 1941 Bernheim,³⁵⁴ studying the metabolic activity of the tubercle bacillus, showed that salicylates and benzoates increase the oxygen uptake of nongrowing suspensions of a virulent bovine strain. Lehmann³⁵⁵ subsequently demonstrated that this effect is obtained only with pathogenic

marked protective and curative action in tuberculosis in experimental animals³⁶⁸⁻³⁷⁰ In early progressive, infiltrating pulmonary tuberculosis in man, it is of decided benefit³⁷⁰⁻³⁷¹ Dramatic cures have resulted from its employment in the miliary and meningeal forms of the disease,³³⁷ and in various types of localized tuberculous infection that are readily accessible to the drug³⁷² In chronic caseating pulmonary tuberculosis it is generally ineffective and therefore probably contraindicated because of the risk of toxicity in prolonged administration Results of treatment of 2780 cases are reported

the treatment of many gram-negative infections, particularly of the urinary tract An early attempt to treat typhoid fever with this drug is on record³¹¹ The dosage employed was less than 2 gm (2,500,000 units) daily, and yet the clinical responses were encouraging Welch and Randall⁶⁹ subsequently established the bacteriostatic threshold for *Eberthella typhosa* at 3.6 to 7.2 microgm (6-12 units) per cubic centimeter It has not been until recently that unlimited supplies of the drug became available, and meanwhile streptomycin had come onto the horizon as the drug of choice for the gram-nega-

TABLE 1 Clinical Indications for the Use of Antibacterial Chemotherapeutics

INFECTIVE ORGANISM	PRINCIPAL DISEASE	SULFONAMIDES	PENICILLIN	STREPTOMYCIN	OTHER AGENTS
Beta-hemolytic streptococcus	Various infections	Effective	Drug of choice	Partially effective*	Bacitracin
Alpha-hemolytic streptococcus	Subacute bacterial endocarditis	Partially effective	Drug of choice	Partially effective*	Bacitracin
Anaerobic streptococci	Various infections	Not effective	Drug of choice	Not effective	Bacitracin polymyxin (insufficient evidence)
Staphylococcus species	Pyogenic infections	Partially effective	Drug of choice	Partially effective*	Bacitracin
Diplococcus pneumoniae	Lobar pneumonia	Drug of choice	Drug of choice	Not effective	
Neisseria intracellularis	Epidemic meningitis	Drug of choice	Effective	Not effective	
N. gonorrhoeae	Gonorrhea	Effective	Drug of choice	Not effective	
Bacillus anthracis	Anthrax	Effective	Drug of choice	Not effective	Bacitracin (insufficient evidence)
Clostridia species	Tetanus gas gangrene	Probably effective (insufficient evidence)	Drug of choice	Not effective	Bacitracin (insufficient evidence)
Corynebacterium diphtheriae	Diphtheria	Partially effective	Partially effective†	Not effective	
Aerobacter aerogenes	Chronic urinary infections	Partially effective	Not effective	Drug of choice	Polymyxin (insufficient evidence)
Proteus species	Chronic urinary infections	Partially effective	Not effective	Drug of choice	
Bacillus pyocyaneus (Pseudomonas aeruginosa)	Chronic urinary infections	Partially effective	Not effective	Drug of choice	Polymyxin (insufficient evidence)
Escherichia coli	Various infections (organism normally present in intestinal tract)	Effective	Not effective	Drug of choice	Polymyxin aureomycin (insufficient evidence)
Eberthella typhosa	Typhoid fever	Not effective	Not effective	Possibly effective (insufficient evidence)	Polymyxin and chloromycetin (insufficient evidence)
Salmonella paratyphi	Paratyphoid fevers	Not effective	Not effective	Possibly effective† (insufficient evidence)	
Shigella species	Dysentery	Drug of choice	Not effective	Drug of choice	
Vibrio cholerae (V. comma)	Cholera	Drug of choice	Not effective	Partially effective	
Brucella species	Brucellosis	Effective with streptomycin	Not effective	Effective with sulfonamides	Polymyxin (insufficient evidence)
Pasteurella pestis	Plague	Drug of choice	Not effective	Effective	
Pasteurella tularensis	Tularemia	Possibly effective (insufficient evidence)	Not effective	Drug of choice	

by a Committee of the National Research Council³⁷³ Several general reviews on the clinical use of streptomycin have become available in the past few years⁴⁻³²⁷⁻³²⁸⁻³²⁹⁻³⁷⁴⁻³⁷⁵

The work of Pratt and Dufrenoy,⁸¹ discussed in a previous section, indicated that the action of penicillin is qualitatively similar upon all organisms, except that much higher concentrations are required to inhibit the growth of gram-negative species Indeed most organisms are sensitive to penicillin at some concentration, and the drug is so nontoxic that extraordinarily high levels can be safely maintained in a patient's plasma, and even higher levels in his urine One wonders whether penicillin in "massive" doses might not replace streptomycin in

tive bacteria If one is now willing to use penicillin in the same dosage as streptomycin* a number of pathogens heretofore considered "insensitive" may be found responsive to the less toxic drug

"Superinfection"

A disturbing feature of the clinical use of the chemotherapeutics is the possibility of upsetting normal antibiotic relations between various bacterial species in vivo It is reported, for example, that prolonged treatment with penicillin results consistently in a shift of the bacterial flora of the nasopharynx in favor of the gram-negative species that can flourish in the presence of the drug³⁸⁰ That

*Two grams daily would represent about 3,000,000 units.

fections (chiefly ulcers, carbuncles and chronic osteomyelitis) responded favorably and those due to streptococci and staphylococci, even when these organisms were penicillin resistant, healed dramatically. Further favorable experiences in the local use of the drug are reported by Miller and his collaborators.⁴¹⁴ In neither investigation was toxicity of any kind observed.

Bacitracin has been administered systemically to over 150 patients with a variety of diseases caused by gram-positive organisms, which had failed to respond to sulfonamides or penicillin.⁴¹⁵ In 105 of these cases,⁴¹⁶ the over-all favorable response was about 70 per cent with dramatic cures in some of the streptococcal and staphylococcal infections. Over 100 cases of syphilis have been treated with bacitracin alone or in combination with penicillin,⁴¹⁵ a synergistic effect of the two drugs having been noted in rabbit infection.⁴¹⁷ It is still too early for proper evaluation of these results.

Transient albuminuria and other signs of nephrotoxicity have been observed.⁴¹⁵ These, as was earlier found in animal experiments, vary with different lots of the drug and different production processes. It can be hoped, on the basis of experience with streptomycin, that they will disappear with purification.

The reports cited are promising. The near identity of the antibacterial spectrum of bacitracin with that of penicillin places it at a disadvantage from the standpoint of further development, since it must presumably offer some obvious advantage over the latter. This it may well do in its superior qualities of absorption and excretion, leading to prolonged blood levels, and permitting infrequent injection. Another important advantage is its effectiveness against penicillin-resistant organisms, particularly those which produce penicillinase and thereby nullify the usefulness of penicillin in mixed infections where they are present.

Polymyxin

Polymyxin, isolated by Stansly and his co-workers⁴¹⁸⁻⁴¹⁹ from the soil organism, *B. polymyxa*,⁴²⁰ is a cyclic polypeptide containing d-leucine, l-threonine, d-serine, diaminobutyric acid and a C₂ diamino acid.⁴¹ It displays greatest specificity toward organisms of the gram-negative group, resembling streptomycin in this respect. Noteworthy exceptions are the insensitivity of *Pr. vulgaris* and the neisseria group. The drug is tolerated by animals and man in bactericidal concentrations. Development of resistance has not yet been observed despite attempts to elicit it in vitro — a fact of outstanding importance if borne out by further experience. The chemotherapeutic ratio, determined in mice and dogs by acute and chronic administration, is highly favorable. The intravenous LD₅₀ in dogs is 25 mg per kilogram of body weight, whereas a single intramuscular dose of 5

mg per kilogram produces effective blood levels for several hours.⁴²² Mice are reported to be protected against infection with *K. pneumoniae* and *H. influenzae*.

Systemic administration of polymyxin to 26 patients has recently been reported.⁴²³⁻⁴²⁴ The drug was given intramuscularly in divided doses totaling 0.2 to 0.5 gm daily, usually about 3 mg per kilogram of body weight a day. Plasma levels of 0.6 to 1.3 microgm per cubic centimeter in twelve hours rise gradually to between 2.5 and 5.0 microgm per cubic centimeter after five or ten days of treatment. The drug does not appear in the cerebrospinal fluid, even in meningitis, but can be administered intrathecally. Excretion in the urine is delayed, but at the end of four days about 60 per cent can be recovered. The infections treated included those due to *Ps. aeruginosa*, *A. aerogenes*, brucellas, *K. pneumoniae* and *E. typhosa*. In all these infections some dramatic cures were observed, especially in cases that had been refractory to all other chemotherapeutics. Five cases of pertussis were also treated. The series is too small for statistical evaluation, but it was the impression of the investigators that some of the responses were unquestionably produced by polymyxin.

Serious nephrotoxic effects have been observed. These occur fairly regularly at the higher dosages and consist of albuminuria, granular casts and occasionally azotemia and diminution of the urine specific gravity. The effects may be very transient, disappearing while the drug is continued, or so severe as to necessitate interruption of therapy. As with bacitracin, production methods have a great deal to do with the toxicity observed. The material used for the studies cited above is about 70 per cent pure, and is designated polymyxin D. British workers have employed a material called aerosporin,⁴²⁵⁻⁴²⁷ which is now referred to as polymyxin A. A new product, which does not contain d-serine, is known as polymyxin B, and its toxicity is presently being investigated, the d-amino acid having been observed to be highly nephrotoxic. Minor toxic reactions to polymyxin include drug fever, anorexia and epigastric distress, and eosinophilia in a single patient. No blood dyscrasias, liver disturbances or skin rashes have been noted.⁴²⁸

Chloromycetin

Early this year Ehrlich and his collaborators,⁴²⁹ and simultaneously Gottlieb and his co-workers,⁴³⁰ reported the isolation, from a species of streptomycetes, of a new antibacterial compound containing nonionic chlorine. This substance, named "chloromycetin," has several remarkable properties — an effective oral absorption, unusually low toxicity, high activity against many gram-negative organisms, proved antirickettsial activity under laboratory conditions and early clinical results that are highly promising.⁴³¹

organisms, whether human or bovine. It appeared highly probable that these compounds were being utilized as substrates for respiration, and the effect of a series of structural analogues was investigated. Para-aminosalicylic acid (PAS) was shown to inhibit growth of *Mycobacterium tuberculosis* in vitro at a concentration of $10^{-5}M$. Blood levels of this order could be established by oral administration to animals and man. Lehmann³⁸⁶ reported the treatment of 20 tuberculous patients with doses of 10 to 15 gm daily, giving blood levels of 2 to 7 mg per 100 cc.

Youmans and his associates^{387, 388} confirmed the bacteriostatic effect of PAS at 0.01 to 0.1 mg per 100 cc in vitro but found the toxic dose in mice to be extremely close to that required for effective blood levels. Strains that were sensitive and those that were resistant to streptomycin were equally inhibited. Although survival of treated infected mice was significantly prolonged, all the animals showed tuberculous lesions at autopsy. Very similar results were obtained in rabbits and guinea pigs by McClosky and his co-workers,^{389, 390} who also found mere summation of effects when PAS and streptomycin were combined. On the other hand Vennesland et al³⁹¹ showed striking enhancement by PAS of the bacteriostatic action of streptomycin in vitro.

Feldman and his associates³⁹² obtained impressive cures in guinea pigs when treatment was started six weeks after infection. Although 4 per cent PAS was included in the diet, no toxicity was observed. However, the low blood levels (0.5 mg per 100 cc) suggest that not all the drug was actually ingested and absorbed.

It appears to be the general consensus that PAS is much less effective than streptomycin. However, further clinical trials are under way, and it is conceivable that the drug may be a useful adjuvant to therapy with more potent chemotherapeutics. It would be interesting to explore the possibility of employing PAS during rest periods punctuating an intermittent course of streptomycin.

Subtilin, Subtenolin and Bacillomycin

After Dubos had isolated tyrothricin from *Bacillus brevis*, several groups of investigators turned to *B. subtilis*, another gram-positive spore-forming organism, as a possible source of chemotherapeutic material. Employing Dubos's procedure, Jansen and Hirschmann³⁹³ isolated *subtilin*, a polypeptide that, in contrast to tyrothricin, is rapidly diffusible and considerably more toxic to bacteria than to tissues.³⁹⁴ Its antibacterial spectrum includes the common gram-positive species (streptococci are very sensitive), *M. tuberculosis* and certain pathogenic actinomycetes.^{395, 396} Mouse pneumococcal and streptococcal infection was aborted as late as nine hours after inoculation,^{397, 398} but the experiment reported is inconclusive since both infecting organisms and drug were injected

into the same site (intraperitoneal). The drug also displays affinity for treponemas in vitro but is less effective than penicillin on a weight basis, and even large doses fail to heal the primary chancre of rabbit syphilis.³⁹⁹ Although four years have elapsed since its isolation, no clinical reports on subtilin have appeared, nor are complete animal toxicity studies available.

A surprising number of different compounds have been obtained from *B. subtilis*, all of which show growth-inhibiting activity against micro-organisms in vitro. Only the most promising of these can be mentioned here, a more complete discussion is found in a recent review.⁴⁰⁰ *Subtenolin* is an enolic compound of low molecular weight, active against streptococci and staphylococci and a large group of gram-negative species including *E. typhosa*, *Esch. coli*, salmonella and pasteurella.⁴⁰¹ Mouse-toxicity studies are encouraging, but the drug is still impure and in the early stages of investigation.⁴⁰² *Bacillomycin* is of interest because it is almost devoid of antibacterial action and yet highly toxic for most pathogenic fungi.⁴⁰³

Bacitracin

Bacitracin, also isolated from *B. subtilis*, is a diffusible polypeptide of low molecular weight whose composition differs in two or more amino-acids from that of subtilin.⁴⁰⁴⁻⁴⁰⁶ It resembles penicillin in its activity toward a variety of gram-positive bacteria and spirochetes. Eagle^{399, 407} has shown that the spirocheticidal action differs from that of penicillin and resembles that of the disinfectants in that the rate of killing is proportional to concentration up to the highest levels tested. In rabbits doses far below the toxic suffice to abort syphilitic infection and heal primary lesions. Gravimetrically, it is stated, the drug is less potent than penicillin, but this comparison, as pointed out above, is irrelevant except in relation to the toxicity of each compound. Bacitracin is excreted by glomerular filtration and more slowly absorbed from parenteral sites than penicillin so that its pharmacodynamic properties are highly favorable.⁴⁰⁸ In the dog effective levels persist in the blood for five to ten hours after intramuscular injection of 3000 to 6000 units per kilogram of body weight, a dosage at which no toxic effects are observed.^{409, 410} In mice and rats large doses produced renal lesions (in the former) and convulsions leading to death, but as these effects were not correlated with the antibacterial potency of different lots it seems likely that they were caused by an impurity.⁴¹¹ Like penicillin, the drug is not well absorbed by the oral route, but it is not inactivated in the gastrointestinal tract, retaining activity against susceptible enteric pathogens.⁴¹²

Meleney and Johnson⁴¹³ report favorably upon 100 cases of surgical infection treated topically with solutions or ointments containing 10 to 100 units per cubic centimeter. About 88 per cent of the in-

can be made against a great many such infections despite the lack of an obvious rationale. It is curiously typical of the history of chemotherapy that fundamental understanding of the underlying principles has often lagged behind their practical employment in the treatment of infectious disease

* * *

The recent prodigious advances in antibacterial chemotherapy, whose highlights have been reviewed here, exert a profound influence upon all the biological sciences and upon the practice of medicine. They offer sure promise of a day when harmless drugs of precise specificity will endow the clinician with the power to destroy every pathogen that threatens the life or health of man. To the laboratory investigator, in whatever field he works, the chemotherapeutic drugs are delicately fashioned tools for probing the intimate mechanisms of the life process. By their very nature they lay open the living cell, exposing the complex metabolic patterns upon which *all drugs* must act. This deeper significance of chemotherapy to the whole of pharmacology was never more clearly discerned than by Ehrlich² himself, when he wrote

I am of the opinion that the fundamental question of pharmacology, the question of the combination of drugs and the cause of such combination, will hardly be brought to a solution in the complicated system of the higher organism, rather is it more to the point to study such processes in their purest cellular form, in the simplest of cells

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The antibacterial spectrum of chloromycetin is qualitatively similar to that of streptomycin, although it has low potency against the tubercle bacillus in proportion to its activity against the common pathogens. Parenteral injection in dogs produces local tissue necrosis and certain untoward systemic effects, but this mode of administration is rendered unnecessary by the efficient absorption of the drug from the gastrointestinal tract. Levels higher than 10 microgm per cubic centimeter are easily achieved in dogs and man by ingestion of a 1-gm dose. Larger amounts are tolerated, but rapid absorption and excretion make for familiar difficulties in maintaining constant plasma levels. However, the need for very frequent dosage is not a serious drawback in oral medication. Chloromycetin is about 60 per cent bound to plasma protein at therapeutic concentrations.^{432 433}

Mouse protection and therapy are achieved in a variety of infections. Tuberculosis in the guinea pig could not be controlled, failure to reach effective blood levels (12.5 microgm per cubic centimeter) apparently accounting for the unfavorable results.⁴³⁴ Its antirickettsial action is perhaps the drug's most striking feature. The life of chick embryos infected with the agents of typhus and scrub typhus was unquestionably prolonged, in one experiment, although all controls died eight days after infection, eight of twenty-four embryos hatched on the fifteenth day.⁴³⁵ Doses of 50 to 100 mg per kilogram of body weight clear the lesions of rabbit syphilis, but only temporarily.⁴³² However, it is not stated whether this was the maximum tolerated dose.

Organisms sensitive in vitro to less than one microgm per cubic centimeter include *Borrelia recurrentis* (0.00625 microgm per cubic centimeter), brucella, *E. typhosa*, *Esch. coli*, *H. pertussis*, *K. pneumoniae*, pasteurella, salmonella, shigella, *Pr. vulgaris*, streptococcus and staphylococcus.^{430 432}

The unusual antirickettsial activity led to early clinical trial in scrub typhus. Preliminary data on 5 patients⁴³⁶ were unconvincing, but subsequent reports of 25 treated and 12 untreated patients show an impressive reduction in the duration of fever, and an average shortening of hospital stay from thirty to nineteen days.⁴³⁷ As against 2 complications and 1 death in the control group, no complications or fatal cases occurred in the treated group. The dosage employed was 50 mg per kilogram of body weight initially and 200 to 300 mg every two to four hours thereafter to a total dose of about 6 gm. All medication was by mouth.

Equally impressive were the first results obtained in typhoid fever which is notably resistant to other chemotherapeutics. Woodward and his collaborators⁴³⁸ report 10 cases with positive blood culture treated with 19 gm over a period of eight days. On this regime (50 mg per kilogram of body weight initially) blood levels of 40 to 80 microgm per cubic centimeter in the first day fell to a plateau of about

20 microgm per cubic centimeter, which is eighty times the inhibiting level for *E. typhosa* in vitro. Response in all patients was prompt, blood cultures becoming negative and fever subsiding promptly. Treatment was started on the ninth day of the disease, after which the patients treated became afebrile in a mean period of three and a half days, whereas the corresponding period in 8 controls was twenty-six days. However, 2 of the 10 patients treated developed perforation or hemorrhage during the afebrile period.

Aureomycin

In very recent months reports of a new and unusual substance have begun to appear. Isolated by Duggar from a streptomyces species it is named "aureomycin," because of its yellow color. The work dealing in detail with the antibacterial spectrum of this compound and its toxicity in animal experiments^{439 440} is not yet in print at this writing. Aureomycin is said to be effective against streptococci and staphylococci, *Diplococcus pneumoniae* and several gram-negative species including *A. aerogenes*, *K. pneumoniae*, *H. influenzae* and the brucella group.⁴⁴¹ In this respect the drug resembles streptomycin. Unlike the latter, it also displays marked antirickettsial action and, uniquely, is also effective against certain virus infections.⁴⁴²

Aureomycin has been used locally in 0.5 per cent solution for the treatment of a variety of ocular infections.⁴⁴³ In the opinion of the investigators, it was at least as effective as penicillin in the cure of staphylococcal conjunctivitis, and was also strikingly curative in a number of conditions known or presumed to be viral in origin. No irritation or other toxic effects were observed.

Excellent response is reported in a small series of patients treated systemically with aureomycin.^{441 444} These include cases of brucellosis, typhoid fever, urinary-tract infections caused by the coli-aerogenes group and *S. faecalis*, and other bacterial infections. The most remarkable results⁴⁴⁵ were obtained in Rocky Mountain spotted fever (14 cases), typhus (Brill's disease) and scrofula.

The antiviral properties of the new drug were demonstrated⁴⁴² by an impressive protection of mice infected intracerebrally with lymphogranuloma inguinale. In 25 patients with this disease, treated by the daily intramuscular injection of 10 to 40 mg of aureomycin, improvement was seen in all. In 8 patients with buboes, there was a definite reduction in bubo size after four days of therapy and a parallel disappearance of elementary bodies from tissue cells. Similarly encouraging results were obtained in cases with proctitis and rectal stricture. These results were obtained despite the absence of a detectable aureomycin level in the blood.

The proved efficacy of chloromycetin in rickettsial and of aureomycin in both rickettsial and virus disease leads one to hope that real inroads

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

CASE 35051

PRESENTATION OF CASE

A fifty-three-year-old woman was admitted to the hospital because of nausea, vomiting and abdominal pain.

Ten years before admission, eight hours after a lobster dinner, she suffered an attack of "acute indigestion" with sudden, sharp pain in the epigastrium, nausea and vomiting, she recovered by the next day. Eight years before admission she had a similar attack following another lobster meal. Five years before admission she had dull, epigastric pain with nausea and vomiting after an evening meal at which cantaloupe had been one of the items on the menu. Two months before admission she had a short, similar attack following corn on the cob. Thirty-six hours before admission, following breakfast of orange juice and coffee, she noted dull, left, epigastric pain, which soon moved to the right side. She became nauseated and vomited the breakfast. The pain spread toward the umbilicus and was "like something wanting to get through but couldn't." She continued to vomit whenever she took any water. At noon an enema was productive of large amounts of brown feces. She continued to vomit in the afternoon and evening whenever she took liquids. The next day she was able to retain tea and water. The dull pain around the umbilicus persisted. She had no bowel movements and passed no gas by rectum. There was no vomiting, but she did feel nauseated. No history of chills, fever or jaundice was obtained.

On physical examination the chest was clear. The patient was quite comfortable when lying in bed, except when she moved, and then there was pain around the umbilicus. The abdomen was tense and distended, and there was periumbilical tenderness. The peristaltic sounds were low-pitched and active. No masses were palpable. Vaginal and rectal examinations were negative.

The temperature, pulse and respirations were normal. The blood pressure was 110 systolic, 70 diastolic.

Examination of the blood showed a hemoglobin of 14 gm and a white-cell count of 21,000, with

86 per cent neutrophils. The platelets appeared to be increased in number. The urine showed a +++ test for albumin and a few hyaline casts in the sediment.

On the evening of the day after admission the rectal temperature was 101°F, and the pulse 120. There had been no change in the type of pain. The patient had retained all fluids taken during the day. There had been no bowel movements since admission, nor had any gas been passed. The abdomen was more distended, and there was slight bluish-red periumbilical discoloration. The abdomen was tympanitic. There were no peristaltic sounds, and only a few high-pitched, metallic tinkles were heard. On the third hospital day the temperature had returned to normal. The patient ate some food and vomited bile several times. The abdomen was less tense since an enema was given with the return of a small amount of feces.

Another urine examination revealed a + test for albumin. The white-cell count was 9800, with 90 per cent neutrophils. The serum nonprotein nitrogen was 42 mg, and the total protein 5.7 gm per 100 cc. The van den Bergh test was 0.5 mg per 100 cc direct and 0.8 mg per 100 cc total. The amylase was 70 units, the prothrombin time was 22 seconds (normal, 16 seconds). The chloride was 88 milliequiv per liter.

X-ray studies were reported as follows:

The gall bladder concentrates the opaque dye moderately well. There are two nonopaque stones, 8 mm in diameter, in the gall bladder. Barium filling of the large bowel demonstrates a narrowing in the sigmoid, 8 cm in length, which is persistent as long as the patient is in the supine position. In this position there is a suggestion of extrinsic pressure on this portion of the sigmoid from the right and from behind. With the patient in the prone position, however, this loop can be made to distend to practically normal caliber. The mucosal pattern of the sigmoid appears to be intact. Just distal to the hepatic flexure there is a second area of narrowing. Here again the mucosa appears to be intact, and the bowel can be displaced by turning the patient into the prone position. The bowel is displaced somewhat inferiorly, apparently by a mass extrinsic to the bowel.

On the fourth day the patient complained of pain over the left lower ribs anteriorly on breathing. A chest x-ray film showed an area of increased density above the left leaf of the diaphragm that was consistent with an infarct. Homans's sign was negative. Dicumarol was started at this point. The next day she appeared improved. Gas was being passed by rectum, the abdomen was softer, and peristalsis was active. The prothrombin time was 17 seconds (normal, 16 seconds), the serum amylase was 34 units. The stool was guaiac negative and bile positive. An intravenous pvelogram was negative.

On the seventh day the temperature rose to 102°F (rectal). There was moderate distention, and a mass, 6 by 4 cm, was present in the right upper quadrant. The mass was firm and nontender, not attached to the gall bladder and had a limited

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in both liver function and pancreatic function. This would have been due to acute pancreatitis and acute cholangitis of brief duration. At least the anatomic basis for that was shown to exist. Some changes in the filling of the large bowel were also observed, and in the examination of the small bowel later on we find the report of what seemed to be extrinsic lumps in the abdomen. Whether these lumps were tumor or whether they were swollen areas resulting from the pancreatitis of fat necrosis and reaction in the mesentery and omentum cannot be told by this sort of x-ray study. All we know is that the bowel seemed to be displaced and the liver distorted by extrinsic masses scattered through the abdomen.

The final complication on the fourth hospital day seems to have been pulmonary embolism, with a small infarct, six days after the illness began. However, she was getting better, and in time more tests and procedures like intravenous pyelograms were possible and the serum amylase had fallen within normal range and the prothrombin time was better. I do not suppose she was given vitamin K or transfusions?

DR SIMEONE: She was not given vitamin K.

DR DOCK: This might be a daily variation in the prothrombin level in our laboratory. I am sure that at this hospital nothing like that could happen. This does represent improvement in the function of the liver. The temperature rose, and again there were signs of distention and paralytic ileus. At this time a mass was felt in the right upper quadrant, which had not been felt before. I take it that at the beginning of the illness the abdomen was difficult to palpate, but the mass was now easy to palpate. This makes it seem much more probable that it was the development of a cyst or some other reaction to pancreatitis than a tumor deeply buried and in a few days coming to the surface. The duodenum was now displaced medially and anteriorly—the second portion medially. One would not expect that something developing around the pancreas in the retroperitoneal tissues would push the duodenum medially. It is surprising. If we did not have the intravenous pyelogram, we would think more of a lesion of the right kidney as the cause of the displacement of the duodenum in the direction indicated. That seems unlikely here.

We come to the further observation of something outside the small bowel, and outside the large bowel, which looked like tumor masses in the mesentery and omentum or local areas of inflammatory reaction and edema, perhaps associated with fat necrosis, if pancreatitis was actually the cause of the trouble. She slowly but steadily got better, but the masses became more and more easily felt and were sharply defined as the illness went on. Again I have to ask if a lipase of 18 units is significant.

DR SIMEONE: It is considered normal.

DR DOCK: Both lipase and amylase determinations were normal at this time. The total protein came down from 5.7 to 4.3 gm per 100 cc, which might indicate that the patient had a good bit of parenchymal liver damage, and which could again have been the result of pancreatitis. At no time was a palpable liver observed, and never any tenderness where the liver margin might be. One might be concerned about the woman's having already had liver disease, ordinary Laennec type, which would lower her prothrombin time and total protein. She had retention of bromsulfalein of significant degree, evidence of liver dysfunction without a palpable liver, which I should expect if the liver damage were recent. The renal function was all right. In general, the patient improved but continued to have fever, which we see in some cirrhotic patients and those with pancreatitis. The patient died suddenly. Since she had had a previous pulmonary infarct, the ordinary supposition would be that this woman in the fourth week in the hospital had died of pulmonary embolism—not an uncommon possibility in a patient with a history like this.

So putting all these things together my own impression is that this woman had acute pancreatitis followed by cyst formation in the neighborhood of the pancreas and perhaps by the development of masses in the omentum and mesentery from fat necrosis. Perhaps also she had Laennec's cirrhosis. Nothing is said about an alcoholic background. I do not know whether or not some of the injury was due to alcohol. I think there is more pancreatitis in patients with cirrhosis than one would get with chance occurrence of the two disorders. So that is not an extraordinary combination of diagnoses. If she had cirrhosis, it is not surprising to have superimposed a recent acute pancreatitis. Those are the diagnoses that I would have made had I seen the patient, and I would have been much less impressed by the possibility of all these being due to cancer with tumor masses in the abdomen. I think it is very unlikely that this was due to a combination of vascular accidents, such as diffuse arteritis. Diffuse arteritis can produce pancreatitis and hepatitis. It can produce acute attacks of bowel obstruction due to interference with the arterial supply to the intestine, with paralytic ileus. So while the possibility exists, it seems to me it is more likely that she had acute pancreatitis, associated with either cirrhosis or chronic gall-bladder disease, that was apparently smoldering along when she died of pulmonary embolism.

DR TRACY B. MALLORY: Is there anything of interest in the x-ray films?

DR STANLEY M. WYMAN: We have a large number of x-ray films, but I really think they are quite confusing. If you would like to see them—

range of motion There was no fluid wave The blood sodium was 130 milliequiv, and the chloride 87 milliequiv per liter A gastric series was reported as follows

The second portion of the duodenum is displaced medially and anteriorly There is rather marked dilatation of the proximal jejunum, with irregularities and coarsening of the mucosal pattern The ileum similarly shows abnormality in pattern, with considerable segmentation of the barium column The small intestine appears ovoid in the left lower and right upper abdomen, as though it might be displaced by masses in these regions

By the fifteenth hospital day the patient had slowly improved The mass in the right side of the abdomen was better defined and not tender There had been some slight diarrhea The serum amylase was 27 units, and the serum lipase was 1.88 units, the sodium was 130.3 milliequiv and the chloride 88 milliequiv per liter The total protein was 4.3 gm per 100 cc The prothrombin time was 36 seconds (normal, 16 seconds) A bromsulfalein test showed 32 per cent of dye retained in the serum (5 mg per kilogram of body weight) The nonprotein nitrogen was 17 mg per 100 cc, the cephalin flocculation test was + in twenty-four hours, and ++ in forty-eight hours By the twenty-fifth hospital day the mass in the right middle abdomen had become much more clearly demarcated The temperature, which had again returned to normal, was now spiking to 102°F On the evening of the twenty-sixth hospital day she was found pulseless and apneic twenty minutes after having been quite well when she had taken her evening nourishment

DIFFERENTIAL DIAGNOSIS

DR WILLIAM DOCK* This is a history of food idiosyncrasy, characterized by acute attacks The trouble was with lobster, melon and corn on the cob, but not knowing how often the patient was exposed to such food, I cannot attach much significance to these complaints If this were the only occasion on which she ate the food and it produced the illness, it would be clear cut It may have been an accidental relation in her mind between illness and the food she was exposed to

The attack thirty-six hours before admission sounds as if the patient had paralytic ileus or acute bowel obstruction Up to this point a number of things might have been thought about This attack might have been due to coronary occlusion, which often produces abdominal rather than chest pain When the patient is found to be distended and the story of obstruction is as marked as this, that is unlikely The question is whether it was paralytic ileus due to appendicitis or some inflammatory condition in the abdomen or obstruction due to adhesions or to tumor or even to volvulus or something of that sort An interesting thing is that she had a normal pulse, temperature and respirations

at that time, which is surprising because one would think that she might have had shock after thirty-six hours of nausea and vomiting and that the pulse would have been fast Usually, if the patient is in this state, even if peritoneal inflammation has developed, the temperature may be low or normal because of shock, but she had no evidence of shock or of fever The hemoglobin was normal, but she had a leukocytosis She also had polyuria However, the temperature eventually did rise, and the pulse went up to 120, so that one can regard this as a febrile illness She has been hydrated and then showed fever and a fast pulse, which can occur with bowel obstruction or an inflammatory lesion In women past fifty, one thinks of such things as gall stone in the small bowel But usually this picture is produced either by adhesions or inflammation, and the commonest cause is appendicitis, less commonly acute empyema of the gall bladder or acute pancreatitis

The patient was not explored, she was merely kept under observation She had evidence of bluish discoloration, which makes one think that the lesion was somewhere around the liver, it was at the level of the umbilicus, and there may have been some hemorrhage there The subsequent course shows that the discoloration did not increase as a bruise might in making its way to the surface We hear no more about it, and we do not know what it means The signs were those of paralytic ileus, with an inflammatory lesion as the cause, and obviously the surgeons did not believe this was appendicitis or some other disease requiring prompt exploration and drainage The patient improved, the obstruction of ileus cleared, and the white-cell count fell The amylase was 70 units One never knows about the amylase It came down later to 27 units, which I take to be normal

DR F A SIMEONE Thirty-five is the upper limit of normal here

DR DOCK Across town it is 50 units, but an amylase level of 70 units is twice the limit of normal here The patient probably had recent trouble in the pancreas Also, the prothrombin time was longer than it should have been, with a fairly normal serum van den Bergh There was evidence of liver disease with some evidence of change in the liver function, with low prothrombin and elevated amylase In a patient with signs of pancreatitis and an elevated amylase, the problem is whether this is simply acute edema or hemorrhagic pancreatitis, or whether it is a complication of carcinoma of the pancreas What about pancreatitis superimposed upon duct obstruction? The patient apparently was quite well because a Graham test could be performed, revealing that the gall bladder functioned well and showed two stones Thus, it is possible for her to have had an episode in which a stone stuck in the ampulla of Vater It might have caused transient disturbance

*Professor of medicine Long Island College of Medicine Brooklyn New York

abscess and extending into the left gutter secondarily

DR DOCK Perhaps she had a retrocecal appendix

DR SIMEONE It was not visualized by x-ray study. The pain began as described — epigastric distress that moved down about the umbilicus, and we then believed that it became shifting pain. Shifting pain is one of the most characteristic things about acute appendicitis so that when the abscess or the mass began to develop we thought seriously of a ruptured retrocecal appendix.

DR DOCK The bluish discoloration around the navel did not sound as important on the wards as on the chart?

DR SIMEONE No, it was not at all striking. The abdomen was never tender. The only tenderness was in the left flank. The tenderness appeared to be in the wall rather than within the abdomen. We were never impressed with the intestinal obstruction. She did not show gas-filled intestinal loops at any examination, but she did have distention.

CLINICAL DIAGNOSES

Intra-abdominal abscess

Pulmonary embolism

DR DOCK'S DIAGNOSES

Acute pancreatitis, with secondary inflammatory masses or cysts

Possible liver cirrhosis or common-duct stone as predisposing cause of pancreatitis

Gallstones (x-ray diagnosis)

Pulmonary embolism

ANATOMICAL DIAGNOSES

Acute pancreatitis, with retroperitoneal abscess formation

Peritonitis of lesser peritoneal cavity

Cholelithiasis

PATHOLOGICAL DISCUSSION

DR MALLORY Post-mortem examination was limited to the abdomen so I cannot give the cause of the sudden episode, although there is very little doubt that it was pulmonary embolism. In the abdomen we found that the lesser peritoneal sac was filled with turbid fluid, and its wall lined with chalky areas of fat necrosis. There were also large retroperitoneal abscesses running down both gutters close to the spine on each side. These also showed multiple areas of fat necrosis. The pancreas lay in the midst of and between these abscesses. The pancreatic duct was patent, it opened into the duodenum from a separate opening in the papilla of Vater. It could not have been occluded by the passage of gallstones. The common duct was not dilated and contained no stones. There were, of course, a few stones in the gall bladder. Our diagnosis was abscess formation secondary to pancreatitis in spite

of the fact that we found so very little involvement of the pancreas itself. The pancreas did show foci of old fibrosis, suggesting a previous episode of pancreatitis.

DR DOCK The appendix was normal?

DR MALLORY Yes. The culture from the retroperitoneal abscess showed a mixture of colon bacilli and staphylococcus, but the fluid in the abscesses was not foul, and we thought it was terminal infection rather than a primary infectious abscess.

DR WYMAN The head of the pancreas was not enlarged?

DR MALLORY No.

A PHYSICIAN What did the liver show?

DR MALLORY Slight parenchymal degeneration — the type called "cloudy swelling." There were minor degenerative changes in the kidneys as well. In acute pancreatitis one sometimes gets quite severe degenerative changes in both liver and kidneys, but they were not present here.

DR SIMEONE We had another patient — a woman who died about a year ago — with the same disease, who formed similar retroperitoneal abscesses at one of her operations. In the case under discussion at operation we scraped out, from one of the abscesses, putty-like material that looked like necrotic pancreas, and I was amazed at post-mortem examination to find that the pancreas was for the most part normal.

DR DOCK This peripancreatic fat necrosis is not rare in patients who die of involvement of the liver. One finds it microscopically very frequently.

DR MALLORY Sometimes the dissection in these cases is extensive. One patient came to the hospital presenting a scrotal abscess, which was eventually traced up through the retroperitoneal space to the pancreas.

DR DOCK Was the bowel noticeably displaced at autopsy?

DR MALLORY Yes.

DR DOCK Did this patient have antibiotic therapy?

DR JOHN T. QUINBY Yes. She was treated with large doses of penicillin and streptomycin in divided doses.

CASE 35052

PRESENTATION OF CASE

A forty-eight-year-old man was well until three months before admission, at which time he developed moderately severe joint pains in the arches of both feet, both knees, the left hip and both elbows. These symptoms were not relieved by salicylates or vitamin therapy. Two months before admission he developed cough, weakness and weight loss. One month before admission he was hospitalized elsewhere. He was not able to eat

this is a plain film of the abdomen. It shows the two opaque stones described. There is a peculiar gas pattern in the right lower abdomen, but nothing more specific that one can see. The spot film from the pyelogram shows normal-appearing kidneys and upper urinary passages, with no evidence of embarrassment but some pressure on the ureter.

DR DOCK: The psoas shadow is very good. One does not see it often in pancreatitis. Usually, it fades out with real pancreatitis.

DR WYMAN: It would make a difference how long it was going on.

DR DOCK: But we have been surprised how many times it is preserved with retroperitoneal tumor in this area.

DR WYMAN: I agree.

The examination of the colon shows the mass described pressing on the sigmoid and overlying the right sacrum. Going back to the original film, the soft-tissue density over the sacrum is not very impressive. These are portable films of the chest taken in an effort to determine the cause of the pain, and there is certainly some fluid in the left costophrenic sinus, laterally and posteriorly, and a suggestion that there might be an infarct in that area. But these are poor films.

DR DOCK: Is the liver shadow dense in the left-hand film?

DR WYMAN: I think this is still dye in the gall bladder.

DR DOCK: That persisted for some time?

DR WYMAN: Two days actually. The most puzzling of these films to interpret are those of the gastrointestinal series. I do not know exactly how to interpret them. These are the films of the stomach, and the fluoroscopist was quite sure that the second portion of the duodenum was displaced medially and anteriorly. It seems a little less impressive to me on the films alone. I would think that the duodenum might be displaced anteriorly.

DR DOCK: The loop is quite large.

DR WYMAN: It is a fairly good-sized loop.

DR DOCK: But no intrinsic change.

DR WYMAN: The mucosal pattern is normal. This spot film shows the loop better. This is a film showing filling of the duodenum and several other films showing a suggestion of a filling defect in the third portion of the duodenum posteriorly, just below the ligament of Treitz. I do not know what to make of it. However, in this film taken in a different projection it is less distinct, I do not know whether this is an apparent defect or a true intrinsic defect. The most difficult thing about this patient to explain is the bizarre appearance of the jejunum and ileum. It shows a wild pattern of mucosa, apparently preserved but abnormal in some ways. It looks thickened with some segmentation in the upper ileum or lower jejunum. I cannot explain the picture.

DR DOCK: You do not think that there will be some retroperitoneal lesion?

DR WYMAN: Possibly, with something involving the small bowel, particularly the duodenum.

DR DOCK: There is no evidence of pancreatic tumor? Nothing you could diagnose pancreatitis on? I still think she had pancreatitis perhaps with liver disease that preceded the pancreatitis and these lumps would be reaction. The things against that are the initial part of the course, — not very stormy and not very febrile, — which one usually sees with a large, diffuse fat necrosis.

A PHYSICIAN: Could it have been appendicitis with abscess and pylephlebitis?

DR DOCK: It is possible that the original paralytic ileus was due to appendicitis. But one does not find an amylase that drops the way this did with appendicitis and pylephlebitis. Amylase changes may occur, but I do not know anything about that. The main reason is the general course of the disease — ordinarily, with pylephlebitis, a stormy, febrile course persists, and the patient is much sicker. It does not sound right to me.

DR MALLORY: Dr Simeone, will you tell us your impression?

DR SIMEONE: This patient was admitted to the hospital with a diagnosis of acute cholecystitis. When we saw her in consultation she did not impress us as having acute cholecystitis because she did not have enough tenderness and spasm in the upper abdomen. She represented an even more confusing picture than is recorded in this history. We did a long series of studies. She complained of pain when asked specifically. However, there were times when she was drowsy during the day. I suppose a great many people become drowsy during the day, but this woman could hardly be aroused. We thought of Addison's disease because of the low chloride and the low sodium, but subsequent studies did not bear that out. She began localizing the mass in the abdomen. It began first as an induration in the right part of the abdomen, well below the costal margin. This mass became better and better defined until it was quite accurately outlined as a round mass, fixed — it did not move with respirations — and extending just below the umbilicus on the right. She then began to develop left-sided abdominal tenderness. We were convinced that we were dealing with an inflammatory lesion because of the displacement of parts of the intestinal tract, the febrile reaction and the white-cell count. Operation was therefore decided upon. On the evening before the day of operation she suddenly died of what we thought was pulmonary embolism. Our working diagnosis during all this treatment was retroperitoneal intra-abdominal abscess due to appendicitis as a first choice and to pancreatitis as a second choice, with a retroperitoneal peritonitis localizing in the right-gutter.

obstruction from cancer the x-ray film is apt to show a breakdown of pulmonary tissue in the form of an abscess cavity. But as we shall see later, no definite cavity is present in the x-ray films in this case, and we are forced simply to assume that a certain amount of infection took place. The next point is the normal white-cell counts and normal differentials, which are stressed frequently throughout this record. Again, I do not believe that they are of significance. I was interested in looking at the record this morning of a private patient in the hospital who has had known cancer for several months with a temperature of 101 to 103°F for at least four weeks. In his case the x-ray study does show an abscess cavity beyond the bronchial obstruction, but his white-cell count this morning is still 9900. It is true, however, that his differential count shows 86 per cent neutrophils and that such a high count was not present in the case under consideration. But, again, I do not believe that there is anything in the blood studies that rules out carcinoma or suggests that another diagnosis such as tuberculosis would be better. In the physical examination there is mention of a patch of bronchial breathing which is of course suggestive of consolidation without bronchial obstruction. But this point does not seem to me of real significance. The blood pressure of 70 systolic, 50 diastolic, is interesting and is of possible significance. I remember that in years past we had cases of bronchiogenic carcinoma that very commonly metastasized to the adrenal glands. But I do not believe that in these cases there was sufficient destruction of the gland substance to account for the persistent low blood pressure. Dr Mallory, is it true that we are seeing fewer adrenal metastases from bronchiogenic cancers these days than in the past?

DR TRACY B MALLORY We still see a good many

DR KING The serum protein was low but not low enough to be of great significance, nor can I get disturbed about the albumin-globulin ratio of 1:1. The prothrombin time of 22 seconds, as opposed to the normal of 16 seconds, is again not really significant. The spinal-fluid gold-sol curve is not helpful. The eosinophil count of 5 per cent on two examinations is borderline, although more attention is being paid to such an eosinophilia than was true in the past. But I do not believe there is anything that points to parasitic disease, periarteritis nodosa or other condition in which an eosinophilia would be expected. The urine examinations are important because of the possibility of a hypernephroma with metastases, but a + test for albumin and a few red cells in the sediment are not sufficient to suggest such a possibility. I checked the textbooks again this morning for the possibility of metastases from a basal-cell carcinoma in order to be sure that my impression that they rarely

metastasize was correct. I find that in Willis's* very recent book on tumors he states that metastases to the lymph nodes are rare and that there is only one case on record in which a basal-cell carcinoma, in the reported case on the forehead, metastasized to bones and lung. That is one case in the literature. I doubt if this is a second one.

Apparently, no search was made for tumor cells in the sputum. This is a little strange in this hospital at the present time. There is no mention of bronchoscopy, and I assume that the patient was too sick for this procedure. There was no indication for intravenous pyelograms.

To date, then, I believe that the evidence is in favor of bronchiogenic carcinoma, and we must now turn to the x-ray films to see what help we can get from them.

DR STANLEY M WYMAN The films were taken with the patient lying on his back, Dr King. That is one reason why they are not of good quality. Probably he was unable to co-operate and too sick to be properly positioned. They do show a sharply defined density in the region of the right middle lobe that ends at the interlobar fissure, with some additional mottled density in the upper lobe, again adjacent to the major fissure. There is some pleural reaction along the chest wall laterally and superiorly. It may be fluid or a thick pleura. This appears to be fairly marked over the apex particularly. The right main bronchus, which is described as being narrowed, can be traced from the carina distally, and the branches going to the lower lobe are fairly well seen. The bronchus going to the upper lobe I cannot see, and I cannot see an obstructing lesion.

DR KING The record says, "right main-stem bronchus."

DR WYMAN I think the report is incorrect. The right main-stem bronchus I can see, and I think I can see the bronchi to the lower lobe.

DR KING When you say "right main-stem bronchus," what do you mean?

DR WYMAN I mean the bronchus as it comes off the trachea.

DR KING I may be wrong, but I thought that the bronchoscopists and chest surgeons talked about the right main bronchus as you have but that when they spoke of the right *stem* bronchus they meant that portion of the right bronchus which is below the upper-lobe orifice and above the opening to the right middle lobe.

DR WYMAN I have not heard of that usage. This is the right main bronchus. The upper-lobe bronchus I cannot see, but I cannot say that it is abnormal because I cannot see it.

DR KING But you can make out a definite narrowing of the right main bronchus?

DR WYMAN No, I do not think I can, that is

*Willis, R. A. *Pathology of Tumors*. 992 pp. St. Louis: C. V. Mosby Co. 1943. Pp. 166-192.

solids and had almost daily vomiting, with abdominal and chest pain. He developed bloody sputum. His course was progressively downhill, and he was transferred to this hospital. He had run a low-grade fever, which did not change with penicillin and streptomycin. The white-cell count was 6450 and 8800.

Physical examination showed an emaciated, pale and dehydrated man. Chest examination revealed dullness to percussion and bronchial breathing over the mid-right chest anteriorly. There were rales over the right-lung field anteriorly and posteriorly. The left nipple was replaced by scabs of psoriasis, and there were other plaques over the trunk and back. The nail beds of the fingers and toes were cyanotic and slightly clubbed. Examination of the joints was negative.

The temperature was 101°F, the pulse 105, and the respirations 20. The blood pressure was 70 systolic, 50 diastolic.

The urine was normal. Examination of the blood revealed a red-cell count of 3,650,000, with a hemoglobin of 11.2 gm., and a white-cell count of 11,300, with a normal differential. A sputum test was negative for acid-fast organisms. The serum protein was 6.12 gm. per 100 cc., with an albumin-globulin ratio of 1:1. The nonprotein nitrogen was 26 mg. per 100 cc. The prothrombin time was 22 seconds (normal, 16 seconds).

X-ray examination of the chest was reported as follows:

There is a large area of increased density which is relatively homogeneous within the right middle lobe for the most part, although a number of nodular areas seem to extend into the right upper lobe. Inferiorly the density is sharply demarcated by the major septum. Superiorly the involved portion of the lung gradually fades into normal-appearing lung structure. There is a suggestion of narrowing of the right main-stem bronchus at the level of the hilus, which may result from encroachment by an adjacent mass. There is probably some fluid in the right pleural space.

X-ray examination of the hands and feet failed to show any evidence of pulmonary osteoarthropathy. The spinal fluid was normal except for a gold-sol curve of 0012332110. An electrocardiogram showed sinus tachycardia and right-axis deviation.

On the third hospital day the temperature rose to 107°F, where it stayed for eighteen hours. During this period the white-cell count was 10,700. On the following day the temperature dropped to 101°F, and over the course of the next few days it gradually rose. On the sixth hospital day the white-cell count was 7600, with a differential of 71 per cent neutrophils, 21 per cent small lymphocytes, 3 per cent monocytes and 5 per cent eosinophils. A gastrointestinal series was negative. Three urine examinations following admission all showed a + test for albumin and an occasional red blood cell in the sediment.

The patient gradually became incontinent and more difficult to arouse. The temperature averaged 103°F. A repeat differential count again showed 5 per cent eosinophils. The skin lesion of the left nipple was biopsied, and basal-cell carcinoma was reported.

On the eighteenth hospital day the patient died.

DIFFERENTIAL DIAGNOSIS

DR DONALD S. KING. The next to the last sentence, "The skin lesion of the left nipple was biopsied, and basal-cell carcinoma reported," reminds me of many O. Henry stories, which have an unexpected "snapper" at the end. But in the case in point this is probably not an important climax.

The diagnosis in some ways seems so obvious that contrary to the usual method of attack I will first set up the obvious diagnosis and then try to pick it to pieces. The strong impression from the first paragraph is that we are dealing with a bronchiogenic carcinoma. The first symptom was joint pain, and the patient is reported as having slight clubbing of the extremities. So-called "acute clubbing" has been present in a number of our cases of bronchiogenic carcinoma, but as a rule in these cases the x-ray film has shown periosteal changes. Such changes were not seen in the x-ray films in the present case, but I still believe that the joint pains can be associated with the lung condition. Such clubbing and joint pain are more common in cancer than in tuberculosis. And the whole clinical picture is more characteristic of cancer. In the first place, the patient was a man of forty-eight years, and this is the right age and sex. The symptoms of cough, weakness, weight loss, fever and bloody sputum could have been those of either tumor or infection. He vomited and had chest pain with the vomiting, but the gastrointestinal x-ray films taken later were normal, and there is no reason to believe that there was disease in the gastrointestinal tract itself. Physical examination showed emaciation, pallor and slight clubbing. On the laboratory side there was anemia, and the electrocardiograms revealed right-axis deviation. This whole clinical picture could have been due to tuberculosis as well as bronchiogenic carcinoma, but as I read the story my impression is strongly in favor of bronchiogenic carcinoma rather than tuberculosis.

But let us not be too sure of the diagnosis and let us take up the rest of the evidence and see if it gives any leads that should change our point of view. First, there is the persistent fever, with at one time a temperature of 107°F for eighteen hours. A persistent temperature of 101 to 103°F is not unusual in bronchiogenic carcinoma in which the growth obstructs the bronchus and infection develops beyond this obstruction. But it seems to me that all we can do is to forget the very high temperature for eighteen hours. It is true that when there is suppuration beyond bronchial

DR ZELLER I do not believe he did. The psoriasis was extremely interesting. It was the chronic hyperkeratotic type with lesions on the palms and soles and, in addition, the lesion of the left nipple was one that I have never seen before in psoriasis. We got the information from the patient's wife that this had repeatedly drained bloody serous fluid, not for months, but for years. For that reason we were quite anxious to have a biopsy from the point of view of Paget's disease of the nipple. Dr Bauer was impressed with that as a possibility because a friend of his had died of severe carcinomatosis as a result of metastases from Paget's disease of the nipple. I do not know whether or not this biopsy diagnosis completely rules that out. We were unable to agree that any diffuse vascular disease played a part in the picture unless the psoriasis were connected with Paget's disease. One other thing the patient's wife also stated that disorientation was a prominent feature of this problem, but this varied when he was in the hospital. He was disoriented a great deal of the time. Neurologic examination did not give any information for localizing the lesion in the brain. He did at the onset have severe left-sided headache, which he did not have when here.

DR KING It could have been a cerebral metastasis.

DR ZELLER We thought there could have been one.

CLINICAL DIAGNOSIS

Carcinoma of lung?

DR KING'S DIAGNOSIS

Bronchiogenic carcinoma, involving particularly right middle lobe

ANATOMICAL DIAGNOSES

Bronchiogenic carcinoma, right middle lobe, with metastases to pleura, liver and adrenal glands

Hydrothorax, right

Bronchopneumonia, slight

PATHOLOGICAL DISCUSSION

DR MALLORY Autopsy showed bronchiogenic carcinoma that involved what we believed was the bronchus to the right middle lobe, although the upper and middle lobes were almost completely fused so at first it looked as if it were a part of the upper lobe. There was rather extensive pulmonary involvement throughout the right lung with spreading carcinoma extending to the pleura, which was studded with nodules at the time of death. There was a considerable hydrothorax—nearly a liter of fluid. Metastases were found in the hilar mediastinal lymph nodes. One adrenal gland was completely replaced with tumor and the other showed several small nodules. However, there seemed to be a fairly reasonable amount of adrenal cortex left on this side so I do not think we are justified in concluding that the low blood pressure was necessarily due to adrenal insufficiency. As I remember, there was no blood sodium determination at any time. We did not have permission to examine the head, and I cannot say whether there were cerebral metastases.

the point To recapitulate — the right main bronchus as it bifurcates from the trachea is poorly seen but is grossly normal I think I can see branches going to the right lower lobe I can make no comment about the branches to the upper or middle lobe There is density throughout the entire region, but I cannot outline a true mass

DR KING How much so-called atelectasis in the upper and middle lobes do you find?

DR WYMAN They do not look particularly diminished in size If anything, the right middle lobe looks smaller than usual, but diminution is not a prominent feature, it seems to me

DR KING Is there any neoplasm in the lower lobe?

DR WYMAN Not to any appreciable degree, certainly

DR KING Is this the right leaf of the diaphragm?

DR WYMAN Yes, this appears to be the right I assume the lower, this one, is the left The relative height is a matter of chance based on the position of the x-ray tube when the x-ray film was taken

DR KING Is there anything in the two spot films?

DR WYMAN Nothing that I can make out.

DR KING You are not helping me a bit

DR WYMAN In summary, this looks like a drowned middle lobe with pleural reaction over the right upper lobe, with possibly some intrinsic disease in the base of the upper lobe, I would consider this to be due to bronchial occlusion primarily

DR KING Probably some fluid in the right pleural space?

DR WYMAN I agree — extending over the right upper lobe

DR KING You think that is fluid and not pleural metastases?

DR WYMAN I cannot possibly say, it could be either It does not look nodular, which is against frank metastasis, but the fluid may be due to metastases I do not see how one could differentiate

DR KING As far as I am concerned, it does not give the impression of tuberculosis Do you want to commit yourself?

DR WYMAN I would be much surprised if it were tuberculosis

DR KING This particular nodule seems important to me since I think it is a characteristic tumor nodule

DR WYMAN If I saw it alone in the left chest, I would be happy to say metastatic disease, but together with the extensive process in the right lung, I could not be sure that it is tumor

The other films are not very contributory The feet and hands show no periosteal reaction The stomach and the duodenal cap appear normal

DR KING There is no periosteal change in these bones consistent with what we call acute clubbing?

DR WYMAN No definite change in the terminal phalanges either I cannot draw any more conclusions from the chest films than you can because they are so poor, but we have to suspect an occluding bronchial lesion of the right middle lobe, with possibly intrinsic disease in the upper lobe

DR KING The left upper lobe is normal?

DR WYMAN Grossly normal The patient is turned quite a way around, and the mediastinal shadow overlies it, but it looks fairly clear to me.

DR KING That was the best conclusion I could draw from the x-ray films — that there was evidence of obstruction to the right middle-lobe bronchus These shadows close to the spine are not masses, are they?

DR WYMAN It is impossible to be accurate. I think it represents heart shadow in addition to transverse processes of the spine

DR KING I cannot make a completely satisfactory diagnosis The main question is whether this was primarily a malignant tumor or primarily infection or a combination of cancer and suppuration or cancer and tuberculosis All I can say is that to my mind the evidence points toward bronchiogenic carcinoma involving particularly the right middle-lobe bronchus I have been over in my mind all the unusual infections and tumors but can see no evidence for any of them

DR JOHN W ZELLER The surgeons who had charge of this patient very astutely, I do not know whether correctly or not, wondered if he had diffuse vascular disease or connective-tissue disease They probably wondered that on the basis of the fact that the man had psoriasis There was a definite history from the family that he did have swollen, red joints at one time Dr Bauer and I, who saw him repeatedly, did not find any evidence whatever for the diagnosis of rheumatoid arthritis or periarthritis nodosa or the other group diseases

DR KING Did he have clubbing?

DR ZELLER I do not believe he did. The psoriasis was extremely interesting. It was the chronic hyperkeratotic type with lesions on the palms and soles and, in addition, the lesion of the left nipple was one that I have never seen before in psoriasis. We got the information from the patient's wife that this had repeatedly drained bloody serous fluid, not for months, but for years. For that reason we were quite anxious to have a biopsy from the point of view of Paget's disease of the nipple. Dr Bauer was impressed with that as a possibility because a friend of his had died of severe carcinomatosis as a result of metastases from Paget's disease of the nipple. I do not know whether or not this biopsy diagnosis completely rules that out. We were unable to agree that any diffuse vascular disease played a part in the picture unless the psoriasis were connected with Paget's disease. One other thing the patient's wife also stated that disorientation was a prominent feature of this problem, but this varied when he was in the hospital. He was disoriented a great deal of the time. Neurologic examination did not give any information for localizing the lesion in the brain. He did at the onset have severe left-sided headache, which he did not have when here.

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THIS AMA — WHAT IS IT?

THE American Medical Association, like any important policy-making body that represents a vital activity, is the recipient of varying degrees of criticism. This solicitude increases when large interests are at stake, as at present, it comes from the press, from elements in the general public, from the medical profession itself.

Such criticism is not to be taken lightly or too readily condemned. Criticism is healthy, it is good for the personal and the corporate soul if constructive and properly directed. Criticism may become the motive power of desired action. Destructive criticism, however — and that is the kind most often encountered — harms many and helps none, aired in public, it creates confusion and distrust in

the minds of those who are frequently not in a position to weigh the evidence or even to know the facts.

Certain questions might be asked of the critics within the ranks of medicine, most of whom believe that they have just complaints, and derive a feeling of pleasure or a sense of importance from proclaiming them. Do they read the Organization Section in the *Journal of the American Medical Association*? In particular, do they read the proceedings of the House of Delegates as published? Do they know who their own delegates are, and do they discuss with them national medical problems? Do they attend their district-society meetings and take any active part in discussing and formulating the policies that they would like to see officially adopted? Do they really know what they are talking about?

Perhaps at this point it might be pertinent to ask just what the American Medical Association really is.

The American Medical Association, gentle reader, if you are a member of your state medical society or your Fellowship in the Massachusetts Medical Society, for instance, makes you automatically one of the 136,000 members of the American Medical Association. You may further, on application to the American Medical Association and on payment of a modest assessment that entitles you also to receive the *Journal of the American Medical Association*, become one of the 76,000 fellows of the organization, eligible to hold office in it and to participate in the work of the scientific sections.

As a fellow you have the privilege of helping to support this organization whose only object of existence is to improve the quality and standards of medical practice. This it constantly works toward through the House of Delegates (your representatives) and the Board of Trustees, through the Judicial Council and the councils on medical education and hospitals, scientific assembly, medical service, pharmacy and chemistry, physical medicine, foods and nutrition, industrial health and national emergency medical service. It does so through the bureaus of health education, legal medicine and legislation, exhibits, investigation, industrial and personal relations and medical economic research. It

serves you and the public through the committees on scientific research, therapeutic research, medical motion pictures, rural medical service, scientific exhibit and therapeutic trials, through the scientific sections and the publications

Being composed of human beings — you and other physicians like yourself — your association may sometimes err in judgment, and may often seem to move too slowly when a swift and unerring decision is needed. If this appears to be the case, discuss the matter in your district society and with your delegates. No good can be accomplished by passing the word of your disapproval up and down Main Street. The only possible result will be a general conviction that the doctors don't know how to run their own business and someone had better do something about it.

If your association in your opinion is at fault then start the correction from within. As so aptly stated, some centuries ago, "It is a foule byrd that fyleth his owne nest."

MEDICAL PRACTICE IN GREAT BRITAIN

ENGLAND's current National Health Service Act that came into effect on July 5, 1948, did not, as Sweet points out elsewhere in this issue of the *Journal*, inaugurate any sudden and explosive change in the distribution of medical care in that country. It was rather the latest step in a series of changes that began with the National Health Insurance Act of 1912. By that act a system of compulsory health insurance was established for nearly all wage earners, resulting in the provision of both medical service and medicines to approximately a third of the population.

In 1929 the Local Government Act increased the number of hospital beds operated by the Government, and in 1936 the Voluntary Hospitals Paying Patient Act opened these institutions to the entire population, whether able to pay or not. During the war years Mr. Churchill's minister of health, in conference with representatives of the medical profession, entered into an agreement for a service to cover all aspects of medical care for almost the whole nation. Mr. Aneurin Bevan, minister of health of the Labour Government, took the next step and put through the present Act

against the opposition of the profession, precipitating the confused and controversial situation that exists today.

The position in which the physician may find himself as a result of this confusion is relatively unimportant and is not the issue at stake in Great Britain or in any country that may choose compulsory insurance as its method of providing a wider distribution of medical care. The real issue is the quality of the service that he will be able to deliver under changed and more difficult conditions of practice.

The situation in England does not necessarily carry any implications of what might happen in the United States were the Government to embark on any scheme of compulsory health insurance. The temper and discipline of the people and economic conditions in the two countries are vastly different, and it may be assumed that the quality of medical education and practice in England has suffered greatly since the beginning of the war. Moreover, conditions of practice in England are almost certain to improve as the country becomes adjusted to its regimen.

Perhaps a system of compulsory health insurance in the United States would be less undesirable than many persons now fear, it is natural, however, that the risks inherent in the change to a system that has apparently worked so poorly elsewhere should be dreaded. Slowly as the social aspects of medical care have developed in this country, under a system of free enterprise — much more slowly than the science of medicine has overtaken its horizons — there is still delivered here the best medical care in the world, and it must not be put in jeopardy without better assurance than has yet been offered that the proposed changes represent an improvement. Every instinct must cry out for caution.

As Dr. Edward D. Churchill recently affirmed, this country, like the rest of the world, is in the midst of a social revolution of which a changing type of medical practice represents only one phase. Already the federal Government is paying a medical bill of \$1,200,000,000 a year, over four fifths of it for the care of the patient. Further crystallization of medicine under Government control could easily inactivate its progress in a phase of evolution that

may well result, if allowed to continue its way unhampered, in a more simplified system of practice with much greater emphasis being successfully placed on the prevention of disease and the improvement of health

"IF YE BREAK FAITH"

DURING nearly sixty years of his long and singularly useful life, Dr Walter P Bowers, first editor of this *Journal* under the ownership of the Massachusetts Medical Society, was associated with the Clinton Hospital Under his guidance it grew from a modest nursing home to a general hospital serving Clinton and its surrounding communities

No task was too humble for Dr Bowers's conception of community service As chief surgeon of the hospital he was not above serving as orderly when the occasion required, wheeling his patients to the operating room, carrying them from the truck to their beds As the hospital outgrew and wore out its facilities for discharging its obligations to the area it serves, in 1944 he set his hand to his last task as president of the Hospital, at the age of nearly ninety, in the collection of a fund for a new hospital building This fund was oversubscribed, but rising costs did not permit the completion and equipment of the building

The story and the present needs of the hospital are told elsewhere in this issue of the *Journal* in a communication from Henry F Bigelow, who succeeded Dr Bowers as president of the Clinton Hospital

Funds for the completion of the memorial building have been made available by the federal Government in the stated ratio to community effort, and on his death in 1947 it was disclosed that Dr Bowers had left the sum of \$100,000, nearly all his life savings, as his final contribution to the welfare of the communities that he had spent his life in serving This bequest cuts to a relatively modest sum the amount needed to make the federal grant effective and bring the Walter P Bowers Memorial to completion

Even in these unsettled days there can be no thought that the citizens of Clinton and its surrounding countryside and Dr Bowers's other friends will permit this vital enterprise to fail

BIBLIOGRAPHIA INTERMINATA

THERE has been a growing tendency among American men of letters (medical) finally to seal the products of their pen with that last authoritative stamp of literary righteousness, the replete bibliography Like the tail of a kite or the ballast on a yacht's keel it hangs there, keeping its vehicle right side up by sheer weight alone

The *Journal*, as much as any other medical periodical, has been guilty of failing sufficiently to discourage this tendency so universal among today's medical authors It has seemed unkind to criticize the tangible result, in 6-point type, of so much labor

The editor of the *Journal of the American Medical Association* is more forthright In his opinion

It is no longer excusable to bolster a report of a case or an article with a compilation of references to all similar cases that have been reported in the literature The growth of medical literature has made this not only a useless but also an unwarranted task Reference should be given only to articles that illuminate the subject To republish long bibliographies taken from other authors is a form of plagiarism which burdens the literature with uninteresting and worthless lists of titles¹

The *London Lancet*, keen-edged as at any time in its century and a quarter of existence, has noted this transoceanic tendency and commented on it, not unkindly²

[²⁷, ³⁸, ¹¹⁶ think that⁴⁶, ⁷⁶ this method,³, ³² ³⁴ ³⁰³ of citing references⁸ to published papers¹⁶, ⁴², ⁹⁶, ¹¹⁷ is rather over done²¹, ⁷⁴, ¹¹⁰ by some workers,⁹¹, ¹⁴² ⁴⁰⁵ ⁶¹² particularly American authors²⁵, ³⁸ ⁷⁶, ⁸⁵, ¹¹², ²¹⁰ ⁶¹² of review articles, et al

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NOTES FROM THE MEDICAL EXAMINER

THE APPLICATIONS OF SPECTROPHOTOMETRY TO MEDICINE

The development of simple, reliable ultraviolet and visible spectrophotometers within the last ten years has made available an analytical tool of great versatility and power The role played by spectrophotometric methods in research on vitamins and hormones has been spectacular¹ the application of these methods to analytical procedures promises to be equally impressive

Spectrophotometric methods possess certain advantages that are particularly desirable in toxicologic investigations the results are subject to qualitative interpretations having fundamental structural chemical significance, they are quantitative, the procedure is direct and simple, and the results reproducible, and the sample is not consumed

Spectral curves are obtained by the plotting of variations of optical density of the solution with respect to wave length of light In the ultraviolet and visible regions such curves are characteristic of certain molecular configurations, generally involving chemical unsaturation The benzene and pyridine rings, or the benzoyl and phenol groups, are typical easily recognizable structural entities Compounds containing such groups will generally exhibit absorption spectrums closely related to the parent groups

Quantitatively, spectrophotometric methods depend upon the same laws as visual colorimetry the optical density of the solution is proportional to the amount of material present The ability of a chemical to absorb light of a given wave length is expressed by the molecular extinction ϵ , which is the optical density of a molar solution in a 1-cm light path The greater the molecular extinction of the compound, the more sensitive becomes the spectrophotometric method for its detection Useful molecular extinctions in the ultraviolet region range from values as low as 200 to as high as 50,000 These generally permit determination of a compound when present in the order of 100 to 1 microgm

In practice it is rare that a determination of a compound can be made by the light absorption at a single wave length without interference from absorption by other chromogens If the interfering chromogens cannot be removed readily by chemical or physical means, it becomes necessary to evaluate their contribution to the total light absorption This is most frequently accomplished in a two-component system by a second determination of optical density at a wave length chosen because the contributions of the two components to the total density are inversely related²

Carbon Monoxide

Advantages of spectrophotometric methods over conventional gasometric methods are well illustrated in the determination of the degree of saturation of blood with carbon monoxide Gasometric methods, although of high precision when carried out on fresh blood under ideal routine conditions, are laborious, technically difficult and, in the examination of putrid blood, inaccurate Reasonably precise, inherently accurate analyses can be achieved by any of several spectrophotometric means, none of which are technically difficult²⁻⁴ The method of Schmidt,⁴ in which the spectral characteristics of carboxy-hemochromogen are employed, appears to be applicable even to putrid blood

Barbiturates

The simplicity and sensitivity of spectrophotometric procedures are illustrated by recent methods for the detection and determination of barbiturates and thiobarbiturates in blood Pentothal, a thiobarbiturate, exhibits a pronounced absorption band at 288 microns in ether⁵ and 285 microns in chloroform,⁶ and a related band at 305 microns in aqueous alkali⁶ By very simple extractive procedures it is possible to estimate as little as 0.35 mg per 100 cc of pentothal in 1 cc of plasma In the detection of the barbiturates the fact that ϵ at 240 millimicrons changes from 0 at pH 2 to 10,000 at pH 10 has formed the basis of a relatively specific method in which the interference of other chromogens is reduced to a minimum⁷

Phenols

Phenol exhibits strong ultraviolet absorption in acid solution When the solution is made basic the absorption peaks shift toward the visible end of the spectrum The influence of pH on the character of the absorption curve can serve both as an important factor in identification and as a basis for quantitation

Salicylic Acid

This acid, closely related to phenol, is of importance clinically and in many medicolegal deaths It may be estimated by the barbiturate method of Walker, Fisher and McHugh⁷ When it occurs together with barbiturates in blood, it may be separated from them by extraction of a chloroform solution with an aqueous solution buffered at pH 7

Alkaloids

Many of the common alkaloids exhibit useful absorption spectrums in the ultraviolet region^{8,9} Morphine, which has a phenolic structure, possesses a corresponding spectrum The spectrum of nicotine is closely related to that of pyridine and nicotinic acid^{1,9} Ultraviolet spectrophotometry is one of the most convenient and sensitive methods for its detection and determination The ultraviolet absorption spectrum of cocaine appears to be due to the benzoyl group, and the spectrums of atropine, hvocynamine, ephedrine and amphetamine to the substituted benzene ring Strychnine, brucine and quinine likewise possess characteristic and useful spectrums

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JOSEPH T WALKER, PH D
Associate in Legal Medicine
Harvard Medical School

MISCELLANY

AMERICAN HOSPITAL ASSOCIATION

The American Hospital Association, according to the *New York Times*, representing the majority of the nation's hospitals, has gone on record as opposing any further extension of Government supervision in the health field. All legislative proposals to date, including the "Nation's Health" report of Federal Security Administrator, Oscar R. Ewing, were described as "administrative monstrosities" by George Hughes, executive director of the Association. Declaring that administration was the important factor in the health plan, he said that, "The confusion in the present federal activities is not an incentive to turn over to the government all the health activities of the nation."

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I hope that you will consider it quite proper for me to bring this matter to your attention as I have. All of us in Clinton and in the surrounding towns that make up our hospital area of 25,000 people are serious in our purpose to complete this lasting memorial to a truly great physician and citizen, and we would like to offer this opportunity to others who may be of the same mind to give us a lift in this undertaking.

HENRY F BIGELOW, Chairman
Memorial Gifts Committee

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(Notices concluded on page xvii)

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ELECTROSHOCK THERAPY IN DEPRESSIVE STATES*

Experience in a General Hospital

SIMON STONE, M D †

MANCHESTER, NEW HAMPSHIRE

SINCE its introduction by Cerletti and Bini¹ in 1938, electroshock therapy has become an accepted therapeutic procedure and has replaced metrazol as the most effective therapeutic convulsive agent. It has been found most useful in depressive states of a manic depressive nature, involutional depressions and involutional paranoid conditions and in depressions of later life and also as an adjunct in the treatment of psychoneuroses with depressive coloring. It has replaced insulin in the treatment of some early cases of schizophrenia, and has been used experimentally in a large variety of neuropsychiatric conditions including general paresis,² Parkinson's disease,³ tics,³ stammering,⁴ drug addiction and alcoholism,⁵ with indifferent results in many cases.

Electroshock treatment has been mostly limited to state psychiatric institutions and private psychiatric hospitals and occasionally ambulatory office treatment of well behaved, co-operative patients. The office treatment has been frowned upon,⁶ however, in view of the inadequacy in most cases of office facilities for close supervision of patients during and after treatment and the danger of an unexpectedly fatal outcome or the development of severe complications. Such emergencies as respiratory embarrassment, acute disturbed postconvulsive states, fractures or dislocations may be difficult to manage in a physician's office. Authorities in general hospitals have also been reluctant to admit any patients even with mild psychiatric disorders for psychiatric treatment, although the same patients were frequently admitted for a surgical procedure or medical care without hesitation. The reason usually given was that adequate facilities were not available for proper care of such patients in the hospital, and also that the presence of these patients might become upsetting to others. Although it must be admitted that hospitalization of an

agitated patient for prolonged psychiatric treatment in a general hospital in the present crowded condition of such hospitals might arouse justifiable criticism, the hospitalization of a patient for a course of electroshock therapy for a period of ten days or two weeks should not be considered any different from hospitalization for a surgical operation. The urgency is just as great in one case as in the other, and in the communities where no adequate private psychiatric facilities exist this is at times a godsend.

The Elliot Hospital in Manchester and the Concord Hospital have been accepting patients for electroshock therapy for several years, and so far the hospital authorities have had no reason to regret this decision. It was found that some patients in a mildly agitated and apprehensive state could be safely handled in a ward or in a private room till after the first or second electroshock treatment. Usually, the agitation subsides after a few treatments and the improvement that follows often makes close supervision unnecessary.

The advantage of treatment in a general hospital is that any additional studies such as electrocardiograms, x-ray studies and urine and blood examinations can be carried out whenever indicated, without the need of transferring the patients to a general from a psychiatric hospital for such studies as is occasionally the procedure. Also, services of consultants, including cardiologists, orthopedic surgeons and bronchoscopists, are readily available if the need should arise. The fact that the depressed patient can enter a general hospital for special treatment has acted as an emotional booster after recovery has taken place, in that it helped to remove the stigma of admission to a specialized "insane" hospital for treatment, and the emotional trauma that is occasionally associated with such an experience is thus obviated.

The psychiatrist benefits from the hospitalization in that any psychotherapy indicated can be carried out while the patient is in the hospital, and the hospital resident medical and nursing staffs

*Presented at the annual meeting of the New Hampshire Medical Society, New Castle, New Hampshire, June 2, 1948.
From the Neuropsychiatric Service, Elliot Hospital.

†Neuropsychiatrist, Elliot Hospital; neurologist, New Hampshire State Department of Health; neurologist, New Hampshire State Hospital, Concord.

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ELECTROSHOCK THERAPY IN DEPRESSIVE STATES*

Experience in a General Hospital

SIMON STONE, M.D.†

MANCHESTER, NEW HAMPSHIRE

SINCE its introduction by Cerletti and Bini¹ in 1938, electroshock therapy has become an accepted therapeutic procedure and has replaced metrazol as the most effective therapeutic convulsive agent. It has been found most useful in depressive states of a manic depressive nature, involutional depressions and involutional paranoid conditions and in depressions of later life and also as an adjunct in the treatment of psychoneuroses with depressive coloring. It has replaced insulin in the treatment of some early cases of schizophrenia, and has been used experimentally in a large variety of neuropsychiatric conditions including general paresis,² Parkinson's disease,³ tics,³ stammering,⁴ drug addiction and alcoholism,⁵ with indifferent results in many cases.

Electroshock treatment has been mostly limited to state psychiatric institutions and private psychiatric hospitals and occasionally ambulatory office treatment of well behaved, co-operative patients. The office treatment has been frowned upon,⁶ however, in view of the inadequacy in most cases of office facilities for close supervision of patients during and after treatment and the danger of an unexpectedly fatal outcome or the development of severe complications. Such emergencies as respiratory embarrassment, acute disturbed postconvulsive states, fractures or dislocations may be difficult to manage in a physician's office. Authorities in general hospitals have also been reluctant to admit any patients even with mild psychiatric disorders for psychiatric treatment, although the same patients were frequently admitted for a surgical procedure or medical care without hesitation. The reason usually given was that adequate facilities were not available for proper care of such patients in the hospital, and also that the presence of these patients might become upsetting to others. Although it must be admitted that hospitalization of an

agitated patient for prolonged psychiatric treatment in a general hospital in the present crowded condition of such hospitals might arouse justifiable criticism, the hospitalization of a patient for a course of electroshock therapy for a period of ten days or two weeks should not be considered any different from hospitalization for a surgical operation. The urgency is just as great in one case as in the other, and in the communities where no adequate private psychiatric facilities exist this is at times a godsend.

The Elliot Hospital in Manchester and the Concord Hospital have been accepting patients for electroshock therapy for several years, and so far the hospital authorities have had no reason to regret this decision. It was found that some patients in a mildly agitated and apprehensive state could be safely handled in a ward or in a private room till after the first or second electroshock treatment. Usually, the agitation subsides after a few treatments and the improvement that follows often makes close supervision unnecessary.

The advantage of treatment in a general hospital is that any additional studies such as electrocardiograms, x-ray studies and urine and blood examinations can be carried out whenever indicated, without the need of transferring the patients to a general from a psychiatric hospital for such studies as is occasionally the procedure. Also, services of consultants, including cardiologists, orthopedic surgeons and bronchoscopists, are readily available if the need should arise. The fact that the depressed patient can enter a general hospital for special treatment has acted as an emotional booster after recovery has taken place, in that it helped to remove the stigma of admission to a specialized "insane" hospital for treatment, and the emotional trauma that is occasionally associated with such an experience is thus obviated.

The psychiatrist benefits from the hospitalization in that any psychotherapy indicated can be carried out while the patient is in the hospital, and the hospital resident medical and nursing staffs

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From the Neuropsychiatric Service, Elliot Hospital.

†Neuropsychiatrist, Elliot Hospital, neurologist, New Hampshire State Department of Health, neurologist, New Hampshire State Hospital, Concord.

can often be utilized for added indirect psychotherapy. From a teaching point of view, the medical residents can see these patients and follow up their progress and response to treatment. No special facilities are required except a room with a Gatch bed, electroshock apparatus and a nursing team. One nurse assistant experienced in electroshock therapy is sufficient, and usually other nurses can be recruited easily from the regular nursing staff.

The usual number of treatments given to patients that I have treated has been five to seven administered every other day. When electroshock therapy was first introduced it was deemed advisable to administer twelve to twenty treatments as a minimum to most patients in a depressive state. The greatest number of treatments is still being used by many psychiatrists, but I have found that if the patient is going to improve, the major gains generally become apparent after the fourth or fifth treatment and the gain after subsequent treatments is often only minor. I have found it safe to discharge hospitalized patients after such a brief course of treatment, if in the opinion of a responsible member of the family the patient has reached the prepsychotic level. However, in depressed patients with paranoid delusions of long standing a greater number of treatments may be required to prevent a relapse.

The average hospitalization time was about fourteen days for out-of-town patients. Local residents with a satisfactory home environment and an understanding and co-operative family have been treated on an ambulatory basis, the patients remaining in the hospital for several hours after the treatment was completed to assure complete recovery from its aftereffects before they were allowed to leave for home in the company of a member of their family. All hospitalized patients are seen within a week of discharge from the hospital and are followed up at regular intervals. The family is also advised to communicate with the physician immediately if any untoward change takes place in the patient's condition.

I have found electroshock therapy most useful in cases of involutional melancholia and depressive reactions, either manic depressive or reactive depressions. The recovery rate has been raised in these cases, and the duration of the illness reduced about 75 per cent. It is now possible in many cases to abort a depressive attack with five or six electroshock treatments in a period of two weeks instead of the average duration in the past of from six to eighteen months.

Patients with involutional melancholia, who were formerly treated for long periods with estrogens without striking results and who either recovered on their own after several years of illness or finally required hospitalization in a psychiatric hospital, now show an 85 per cent incidence of recovery following electroshock therapy. Relapses have been

uncommon in the cases treated, and in the relapsed cases an unsatisfactory home environment, which often was beyond the psychiatrist's control, contributed to the relapse. Recurrence of depressive attacks in patients treated with shock therapy is not greater than in those who recovered under conservative therapy, and in some patients prone to recurrences this can be aborted by the administration of one or more treatments regularly at monthly or bimonthly intervals.

I have also found electroshock therapy of value in early cases of schizophrenia, in selected cases of anxiety and conversion hysteria, especially those with depressive features, and also in 2 cases of obsessive compulsive neurosis in which the patients failed to improve under conservative therapy, the procedure was used as a remedy of desperation in these cases. In another case the therapy was administered when the patient had failed to improve after prolonged hospitalization in a psychiatric hospital. The obsessive fear of handling knives and compulsion of having to cause harm to members of her family had resulted in the patient's separation from her younger children for several years. The intensity of the fears and compulsions became greatly reduced after five electroshock treatments. In the end she was able to discuss these fears in an impersonal manner, and although they did not entirely disappear she did not seem to be troubled by them to any extent and was able to resume full care of her children.

The oldest patient treated was seventy-two and the youngest twenty years old. Age is no contraindication to treatment, and many depressions of later life respond well to electroshock therapy. One patient had auricular fibrillation and also a right-sided hemiparesis. She was exhausting herself physically from her continuous agitation, impaired sleep and worry over real and imaginary transgressions in the past. The cardiac consultant believed that in view of her poor prognosis without treatment as far as her cardiac condition was concerned, the risk of electroshock treatment was worth taking. She tolerated the treatments well. At the end of a course of six treatments the agitation subsided, self-accusatory ideas disappeared, and she was able to resume her normal activities. Her heart function also improved with the removal of contributing psychogenic factors. The hemiplegia was not aggravated by the treatment, and a constant severe pain in the paralyzed shoulder of which she complained before treatment also disappeared.

There have been no serious complications in any of the cases treated. It is a safe procedure when properly supervised and the mortality is no greater than that for a general anesthetic. In a survey of deaths from electroshock therapy in all American hospitals, Kolb and Vogel⁷ found a mortality figure of 6 per 10,000 or about one tenth the death rate for patients treated with insulin shock. The mor-

tality is slightly higher, however, in curare-treated cases, and many psychiatrists limit the use of curare to patients with suspected brittle bones, pre-existent fractures or extreme muscularity. I have used it only when there was a potential danger of bone fractures or in very muscular patients.

Postconvulsive excited states can be avoided in most cases by intravenous injection of 0.3 to 0.5 gm of sodium amytal about ten or fifteen minutes before treatment. This complication occurred in 2 male patients and was relieved by sodium amytal injections. I have been taking this precaution routinely in strong, muscular persons who showed any evidence of excitement after the first treatment to avoid injury to the patient during this confused state.

Memory impairment is also a frequent transitory complaint, and its severity parallels the number of treatments administered. It usually clears up in a period of several weeks, and impairment is greatest in fields of recall and concentration. Respiratory embarrassment is more common in the curare-treated cases, although I have observed none in the cases I have treated so far. The use of a respirator or artificial respiration generally restores breathing to normal.

No fractures occurred in any of the cases treated. Dislocation of the jaw occurred in the same patient on two occasions and was easily reduced before this patient regained consciousness.

CASE REPORTS

CASE 1 M M, a 21-year-old woman, had felt depressed for about 3 months, lost interest in her friends, slept poorly and expressed death wishes. She planned to be married in a month, but failed to take any interest in the arrangements for her wedding. She also gave up her work at the onset of her illness. Before the present symptoms came on she had had a period of overactivity when she talked excessively, was flighty in her ideas, wanted to be on the go, had many plans, made some foolish purchases and spent her money lavishly.

During the psychiatric interview she was slow in her responses, was unable to elaborate on her symptoms and gave perfunctory answers. She complained of having lost her ambition and said she did not care whether her forthcoming marriage was to take place. She admitted feeling depressed and wishing she were dead. After the second electroshock treatment she talked more freely about herself, appeared more cheerful and showed interest in ward routine and in other patients. After the fifth treatment she developed a mild hypomanic state when she laughed out without evident cause, had a number of plans for her wedding and appeared exuberant and full of energy. This phase subsided in 2 days. She was discharged from the hospital 2 weeks after admission, appearing "like her usual self," according to her parents. She showed good judgment and insight during follow-up interviews and was reported to be in good mental health a year after her discharge from the hospital.

The diagnosis was that of a manic depressive, depressive reaction, with good recovery following electroshock therapy.

CASE 2 L D, a 45-year-old woman with a diagnosis of involutional melancholia had been depressed for about 1 year and had given up her job as a business executive 6 months earlier. She blamed this action on her inability to concentrate, fears of losing her mind and continuous preoccupation and guilt feeling over poor business investments (the last being untrue). She received estrogen injections for over 1

year without improvement. She recovered after five electroshock treatments, and was able to return to work 5 weeks after the treatments were begun. She was treated on an ambulatory basis. She had continued in good mental health for 1 year after the treatments had been completed.

CASE 3 G G, a 49-year-old woman, had been depressed, self-accusatory and apprehensive for 2 years. She became obsessed with many religious ideas, blamed herself for the neglect of her family and refused to allow her husband to go to work for fear of some harm befalling him when he was away from her. She had received estrogenic therapy, various sedatives, and iron and liver for her anemia, without improvement.

When she was admitted she was very apprehensive, and it was doubted whether she could be cared for in a general hospital. Much persuasion had to be used before the first treatment could be given. After this treatment she appeared more relaxed and co-operated well in the other five treatments. She made an excellent recovery after 2 weeks of hospitalization, and has been doing her housework, and her own shopping, which she did not do before admission for treatment. The self-accusatory ideas have disappeared, and she shows good insight. Her husband has also been able to return to his job. As she described it "she has not felt so well for years." She complained of some impairment of memory for several weeks after her return home, which was somewhat annoying at first, but later she found that by taking her time she had no difficulty whatsoever in recalling past events.

The diagnosis was that of involutional melancholia, with good recovery.

CASE 4 J N, a 57-year-old man, developed what he described as a nervous breakdown 2 years previously. He felt discouraged, worried about the loss of his job, failed to enjoy doing things that gave him much pleasure in the past and blamed himself for neglect of his family and his job. He was treated with testosterone, sedation and vitamins, but symptoms continued and he had to give up his job.

He had had a "nervous breakdown" 14 years earlier, which lasted a number of months.

Electroshock therapy was recommended, but he believed that he could benefit more from a few months of rest on a farm. After he failed to improve under this regime, he was given four electroshock treatments, for which he was hospitalized for 2 weeks. He tolerated the treatments well except for a postconvulsive excited period, which lasted for about 10 minutes after the second treatment. He made an excellent recovery and returned to work 10 days after leaving the hospital and has been regularly employed since. The anhedonia and self-accusatory ideas have disappeared, and he enjoys all his former activities.

The diagnosis was that of recurrent depressive reaction with involutional features.

DISCUSSION

It has been estimated that for a community with a population of about 100,000 an average of 12 psychiatric beds set apart in the general hospitals in that community would be a minimum requirement.⁸ When one considers that only about 1 in 5 new patients admitted to a state hospital require care on a disturbed ward, and that early diagnosis and treatment frequently aid in aborting a psychotic attack or reduce its severity so that such a patient can be adequately cared for in a general hospital, it becomes obvious that the better the facilities in a general hospital for the care of such patients, the lighter the burden for the state hospital.

The advantages of general-hospital care are that the hospital staff is greatly reduced for the reason that patients are usually worked up faster and any treatment needed is immediately applied. There has been a tendency in state hospitals because of

can often be utilized for added indirect psychotherapy. From a teaching point of view, the medical residents can see these patients and follow up their progress and response to treatment. No special facilities are required except a room with a Gatch bed, electroshock apparatus and a nursing team. One nurse assistant experienced in electroshock therapy is sufficient, and usually other nurses can be recruited easily from the regular nursing staff.

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PRESIDENTIAL ADDRESS*

DAVID W PARKER, M D †

MANCHESTER, NEW HAMPSHIRE

MANY of the senior group of this society have had the rare opportunity of observing the growth of the art and science of modern surgery from a scope that, judged by present standards, was extremely limited to its present almost unbelievable heights. This development has carried with it serious responsibilities to the surgical profession, and also grave problems in the training of prospective surgeons to cope with the highly diversified and technical procedures that it will be necessary for them to master if they are to take their place as specialists in surgery. There have also been problems of raising the standards of hospital care, expansion¹ of laboratory facilities and refinements of record systems and the limitation of incompetent and unnecessary surgery.

Volumes have been written and published through the years by leaders in the surgical field dealing with these problems. The efforts of the American College of Surgeons and, later, of the American Board of Surgery have been of inestimable value in correcting many of the existing weak spots in the practice of surgery. However, many phases of the situation have not been and probably cannot be, reached by these bodies without a fuller program, and definitely more decisive action by organized groups of surgeons who are in a position to mold the conscience and ideals of surgeons in general in their sphere of influence — for example, the New England Surgical Society in New England.

One hesitates to speak on the training of surgeons before a group who have recently listened to the excellent papers by Lanman¹ and Harvey² on this subject. These men have admitted that the train-

ing of surgeons has become too great a load for the teaching hospitals and although many references have been made to the possibility of training surgeons in the smaller hospitals, no positive action has been taken to supplement these suggestions. After forty years of surgical practice in a smaller community, one develops some ideas on this subject, and I hope to present to you a plan, and I use this word guardedly, that may eventually bring the outlying medical communities into the orbit of teaching institutions.

Until recently, there have been two schools of surgical teaching in this country: the prolonged period of carefully supervised training in teaching hospitals and clinics, and the method of trial and error used by general practitioners to perfect themselves gradually in the art of surgery. It was standard practice some years ago for a physician to begin in general practice and work into surgery gradually, and, had it not been for this self-training, much of the necessary surgery in the smaller hospitals would have gone undone. Today, such a practitioner has to ask a fully qualified surgeon to assist him in operations on appendixes, hernias and gall bladders and up the scale until he has developed enough dexterity to operate fairly safely. And all the while that the senior surgeon is keeping him out of trouble and guiding him through the maze of surgical technic and postoperative care, the novice collects the fee and poses as the surgeon. Today, such a practice is unnecessary, and all too often exploits the surgeon who is asked to assist. The American Board of Surgery and American College of Surgeons have done much to discourage this practice by listing minimal requirements of training before a physician is admitted to the surgical staff of a hospital. But the practice will not disappear until every recognized hospital adheres rigorously to these requirements.

*Presented at the annual meeting of the New England Surgical Society, New Haven, Connecticut, October 1, 1946.

†Surgeon, Elliot Hospital, consultant, Exeter Hospital, Exeter, New Hampshire; consultant, Alexander-Eastman Hospital, Derry, New Hampshire.

shortage of staff physicians and for other reasons to postpone treatment in new admissions till a staff diagnosis is made, which often delays active treatment for some time. At comparatively little cost in even the smaller hospital several rooms can be easily remodeled to give adequate temporary care to any acute psychiatric emergency that might arise without disturbance to other patients. Acute confused and excited episodes are not too infrequent after surgical procedures, or deliveries, in cases of acute cardiac decompensation, anemias and other blood dyscrasias and in cases of cerebral metastatic neoplastic growths. If better facilities were available for the care of such patients in a general hospital, the need for transfer of patients with acute cardiac disorders some distance to a state hospital during a disturbed episode would be avoided. Not infrequently, such patients arrive at the hospital in a moribund condition and die shortly after arrival, much to the chagrin of the state-hospital staff. Attention has been called to this situation and also to the fact that a physician may become liable for malpractice for the unwarranted transfer of a patient to another hospital when the patient's condition is apt to suffer from such a change.⁹ It has been planned, therefore, for at least four rooms to be set apart and equipped at the new unit of the Elliot Hospital for the care of any acute and subacute psychiatric problems that show promise of rapid improvement under proper care.

The mode of action of electroshock therapy is still unknown. Most likely it acts as a bloodless frontal lobotomy, reversible if a moderate number of treatments are given, and just as severe in its aftereffects after too many treatments. The effects are probably not limited to the cortex alone, but also involve the autonomic centers in the midbrain, the pituitary body and, indirectly, the gonadal system. The extinction of undesirable patterns of behavior in animal experiments has been described by Masserman and Jacques¹⁰ after electroshock therapy — at the cost, however, of impairment of some of the higher integrative functions. If the psychosis or neurosis is sufficiently disabling and has not responded to conservative therapy, electroshock treatment appears to be preferable to continuation in the previous state even at the risk of some memory impairment.

There is still considerable divergence of opinion about the value of electroshock therapy in the psychoneuroses. I have seen cases of anxiety neurosis definitely aggravated by electroshock therapy administered elsewhere, improvement was observed after the shock therapy had been discontinued and the patient had been reassured that no more shock treatments were forthcoming and helped toward a better social adjustment, with special attention to sleep and nutritional habits. My impression is that the high rate of improvement reported by some observers¹¹ with electroshock

therapy in cases of psychoneurosis is due to the fact that many of these patients really belong in the cyclic group of disorders, with the symptoms of anxiety and somatic discomforts actually representing a manic depressive, depressive equivalent. Such patients can often deceive even the best trained observer, and the somatic symptoms may be so vividly described and acted out by the patient that the patient often parts with a different organ with each depression at the hands of some eager surgeon. Not infrequently, recovery follows each surgical procedure, as a result either of the effects of the anesthesia (or the emotional release associated with feelings of penance and sacrifice that accompany organ removal in some persons) or the patient's removal to the restful, friendly and solicitous hospital atmosphere from an uncongenial home environment, the recovery may be due to a combination of all factors. These cases are often diagnosed as psychoneurosis, and no doubt the patients benefit from electroshock therapy in that the attacks can be aborted, although the incidence of recurrence is not affected by the treatment. In my own experience electroshock therapy is indicated in about 5 to 10 per cent of cases of psychoneurosis and should then be used only after the patient has failed to improve under a combination of psychiatric treatment, attention to somatic needs, vitamin therapy and betterment of domestic and social adjustment.

SUMMARY AND CONCLUSIONS

Electroshock therapy is a valuable therapeutic agent in cases of involutional depressions, cyclic depressive states, reactive and late life depressions and early cases of schizophrenia. It effects recovery in about 85 per cent of patients with involutional depression and, when administered early, aborts or greatly shortens the duration of manic depressive, depressive attacks, thus aiding in reducing hospitalization time, shortening the duration of disability and preventing suicidal attempts.

It is of value in selected cases of psychoneurosis, and should be used only in resistant cases after other methods of treatment have failed to cause improvement.

The utilization of general-hospital facilities for intramural and ambulatory electroshock therapy has not only brought relief to patients who would otherwise have refused treatment because of their reluctance to enter a psychiatric hospital but also acted as a morale builder to these patients by removing the feeling of ostracism that occasionally is still associated with hospitalization in a psychiatric hospital.

It is recommended that even the smaller general hospitals have one or more rooms equipped for the treatment of acute mildly disturbed psychiatric problems offering a good prognosis and amenable to rapid treatment. Such facilities if more widely

used would eventually aid materially in relieving some of the load in overcrowded state and private psychiatric hospitals

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†Surgeon, Eliot Hospital; consultant, Exeter Hospital, Exeter, New Hampshire; consultant, Alexander-Eastman Hospital, Derry, New Hampshire.

When more and more hospitals close their doors to the surgeon of subminimal requirements, it means that the smaller hospitals are no longer instrumental in training surgeons as they have been in the past, and a correspondingly heavy load is being thrown on the large training centers. Some plan whereby the smaller medical communities can be enlisted again in the training of surgeons who measure up to the high standards that are demanded must now be evolved.

Before any plan is outlined, it must be known what sort of surgeons are to be developed. The surgeon who has completed his residency, qualified for his board examinations and then settled in a large metropolitan area will restrict his surgical practice from the outset to some special field. If he ventures to a community with a small hospital, he will naturally seek to limit himself to surgery, but he cannot be so restricted as his city brethren. He will mainly be a consultant, for patients will not normally turn to him at once, but will be referred by the general practitioners, who see the bulk of patients when they are first taken sick.

The smaller communities cannot support specialists in every field — gynecology, urology, orthopedics, abdominal surgery and so forth, nor can a surgeon expect to keep very busy if his training has been limited to abdominal surgery. From the standpoint of the general practitioner, a surgical consultant must be able to deal with a wide variety of cases if he is to be of any great value to the medical community.

This imposes on the plan of training for the general surgeon a specific obligation, which is not fully recognized, if one is to judge by present trends. More and more, cases are segregated into special services. The young surgeon in his hospital training develops into what might well be called a glorified belly artist. He can remove an appendix or gall bladder and resect a stomach or rectum, but, all too often, the female pelvic organs, the prostate gland and the broken bone are terra incognita. Only if the young surgeon is willing to spend extra years in the larger hospitals can he develop a competence in general surgical work, which the small community needs and the general practitioner demands from the consultant in surgery.

Surgical leaders would do well to insist on rotation through special services by all the young surgeons. This does not mean rotation in menial tasks — a *leitmotif* of intravenous therapy, blood counts and postoperative care — but training that develops both manual dexterity and operating poise in all the common surgical conditions. Under such a system, it would be impossible to produce a situation such as recently came to my attention: a young surgeon had qualified for the American Board of Surgery and yet had no formal training in gynecologic surgery, which comprises 30 to 60 per cent of the practice for the general surgeon in the smaller community.

What I am saying has been expressed repeatedly by leaders in the specialties such as gynecology, obstetrics, orthopedics and urology. These men openly admit that the best practitioners of their particular arts have first of all a broad training in general surgery, so that, whether a man intends to go out to a smaller hospital or remain in the larger centers, his *basic* training should be essentially the same.

The smaller medical community has often glaring deficiencies in surgical service that could well be corrected by incoming surgeons of the younger generation. Perhaps an outside consultant is called in for thoracic cases or difficult fractures or plastic surgery. If the most recent addition to the surgical department can fill any existing gap in surgical talent, his path will be so much easier, and his acceptance by the staff less restrained.

This imposes on the surgeon who contemplates a move to the smaller hospitals the duty of acquainting himself intimately with the medical talents in the community where he plans to practice. Such knowledge will stimulate him to develop special ability in some limited field in addition to his broader training.

Is it possible to fit the smaller hospital into such a program of training? One must not be too impressed by size, for the "sticks" does not so much describe a geographic location as it does a state of mind. It is well to remember that patients in the mountains of New Hampshire and in the fishing villages of Maine have exactly the same diseases as those in Providence or Hartford. Wherever a surgeon takes a careful history, does a thorough examination and makes the necessary x-ray and laboratory studies for an intelligent working diagnosis, sound medicine is practiced, and there the student of surgery can learn and be trained.

A far more delicate subject is the level at which the smaller hospital shall assist in training surgeons. A plan that seems favored by some authors on this subject is to have surgeons train as interns for two or three years in the large center and then finish their apprenticeship in the smaller hospital.

The last part of a surgical training, or the resident stage, is by far the most important. It is the great climax for which all the previous years are but a preparation. The self-confidence, poise and judgment that are essential in the private practice of surgery are developed in this final phase. Smaller hospitals, with their more limited facilities, cannot complete the surgical training nearly as well as the large institutions at the last stage. If they are to be enlisted in the training program, it should be at the level of interns and assistant residents. Any plan that seeks to send men into practice before their training is fairly complete — that is, before their residency has been served — should be discouraged.

Surgery everywhere is a highly competitive field. One reason for this is that surgical fees are propor-

tionately much higher than those in other medical fields. Few of the thousands of doctors in this country who are engaged in private practice can afford to disregard the economic component of their profession. As a corollary, there is competition on two levels in surgery—the professional and the economic. Those who have enjoyed the superior training under men with working ideals usually place the professional consideration of competence first, and these high standards pertain particularly in academic circles. Above all, there is need for a program for training surgeons who can compete with the skills taught them by emphasis on good deeds, and who can succeed so well that they can prosper economically without stooping to unethical practices. All too often the greatest stumbling block in the path of a competent young surgeon who wishes to practice according to the highest ethics is an unscrupulous older colleague who attempts to shut him out.

Such a person may be a good surgeon with a jealous disposition, but usually he is one who uses the knife consistently as a diagnostic instrument of first recourse, and deliberately blames every poor result on the patient's disease. He is willing to continue his indiscriminate surgery even though he clearly realizes his own surgical imperfections.

When such a person (or a group of such men) gains control in a medical community, the place is not favorable to the healthy development of a younger surgeon who may have an excellent training. He is restricted at the outset, every poor result is magnified, and all too often, he is driven in despair to adopt exactly the same methods as his older colleagues.

Let the leaders in the medical centers sound out their young graduates who have settled in the smaller communities, and I am certain that they will find this to be about the greatest obstacle to good surgery that the young surgeon faces.

Some solution to this problem is necessary if openings for the younger generation of surgeons are to be developed, and if the smaller hospitals are to be enlisted in the training program. Here is a problem for the trustees of the hospital. The terrible frustration of talent and training that obtains in many smaller hospitals will not be remedied unless the tactics of the vested interests are curbed by the hospital trustees.

One can expostulate on what should be and on the changes to be made, but no plan that involves the small hospitals will ever succeed without a full and active support from the trustees. There is the power to set standards that will attract the best talent of the community, conversely, if they allow anyone and everyone to do surgery, they will discourage the most competent.

The hospital trustees are selected in various ways, but, by and large, they are local citizens with a record of good business ability. These men are

often fully occupied with their business duties, and the hospital is a charity service that they assume as an obligation to the community. If the bills are paid and the hospital is quiet and clean, they believe that they have discharged their duties, and that the medical profession should be grateful for a place to work. To formulate some policy regarding professional practices in the hospital, they are heavily dependent on the director, who may be a physician, a layman with business training or a nurse who has climbed up from one administrative position to another until she has arrived at that of superintendent. Unless the director or some of the trustees make a special effort to enlighten themselves on such matters as surgical standards and the development of the best practices in the hospital, the staff finds itself floundering in *status quo*.

Hospital trustees need help in the form of sound and impartial advice if they are to keep their hospital apace of new standards in surgery, and if they dare not seek it locally they should find it elsewhere in some competent consultant.

All the things that I have said are by way of formulating a plan for the training of surgeons in smaller hospitals. This purpose will be served best by an integrated plan that utilizes the smaller hospital as part of a training system. Smaller hospitals with such essential facilities as adequate x-ray equipment, a roentgenologist, laboratory facilities and a pathologist should affiliate with larger teaching hospitals. The staff of the parent hospital could serve as consultants to the smaller institutions, and also function as chiefs of service. Clinics and conferences in the teaching hospitals could be open to the staffs of the affiliated groups. By enlisting the support of the trustees for this plan, the smaller hospitals could develop such standards of personnel and practice that they could be trusted to help train interns or assistant residents in rotation from the teaching hospitals. In this way, the new generation would learn much about surgical practice in smaller communities and also find openings for themselves. The trustees might well ask the director of the central hospital to serve on a retainer-fee basis as consultant in local problems that seem difficult of solution.

In his presidential address last year, Dr Lanman¹ hesitated to suggest the formation of another committee. I do not hesitate, but boldly submit that this society choose some members to make a careful study and formulate concrete proposals that can be adopted as a general program to support. The time has come to implement words about training surgeons in smaller hospitals with a realistic and workable plan.

967 Elm Street

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SALT-LOSING NEPHRITIS SIMULATING ADRENOCORTICAL INSUFFICIENCY*

Report of a Case

WILBUR H SAWYER, M D,† AND CHESTER SOLEZ, M D ‡

THORN, Koepf and Clinton,¹ in 1944, reported 2 cases of renal failure simulating adrenocortical insufficiency. They called this syndrome "salt-losing nephritis." Symptoms such as asthenia, weight loss, nausea, vomiting and hypotension were observed and attributed to an excessive loss of sodium and chloride in the urine. Such salt loss was not due to a deficiency of adrenocortical hormones but to disease of the renal tubule, the end-organ on which such hormones act in controlling the reabsorption of sodium and chloride from the glomerular filtrate. The symptoms due to the salt loss were relieved by the administration of sodium, chloride and bicarbonate. The kidneys in these cases were demonstrated to be incapable of normal responses to desoxycorticosterone acetate (DOCA), to pituitrin or to the parathyroid hormone.

The case presented below is another example of salt-losing nephritis simulating Addison's disease. The presence of tanning of the skin, asthenia, weight loss, nausea, vomiting and hypotension, and the absence of cardiac enlargement, eye-ground changes or abnormal urinary constituents led at first to the diagnosis of Addison's disease. This was practically impossible to disprove before death. The presence of severe renal tubular insufficiency, however, with an inability to reabsorb salt in response to DOCA was readily demonstrated.

CASE REPORT

E. T., a 53-year-old married shoe salesman, first entered the hospital on March 11, 1947, complaining of weakness, weight loss and frequent vomiting following meals. He gave a history of mild diurnal frequency (five or six times) and nocturia (four or five times) for several years.

Seven years before admission he had entered another hospital for treatment of a bleeding duodenal ulcer. After this he had been essentially well for about 1 year. He then started experiencing epigastric pain between meals, relieved by food or alkali. Four years before admission he again entered the same hospital, complaining of gastrointestinal bleeding. At that time the blood nonprotein nitrogen was 319 mg per 100 cc, and the urine contained albumin and white and red cells. After 1 month the nonprotein nitrogen had fallen to 92 mg per 100 cc, and he was discharged.

One year before admission he again entered that hospital complaining of epigastric distress. The nonprotein nitrogen was 125 mg per 100 cc, the urine showed a + test for albumin, and the sediment contained a few white cells. Five days later the urine was reported as completely normal. One month later the nonprotein nitrogen was 60 mg per 100 cc, and he was discharged.

Physical examination revealed a thin, pale and weak man. The body weight was 128 pounds. The eye grounds appeared normal. The chest was clear. The heart was not enlarged on physical or x-ray examination. There was some tender-

ness deep in the epigastrium. The skin appeared diffusely tanned. There was no pigmentation of the mucous membranes.

The blood pressure was 120/70, and the pulse 96.

Examination of the blood disclosed a red-cell count of 2,800,000, with a hemoglobin of 8.7 gm (photoelectric-cell technic), and a white-cell count of 10,000, with 59 per cent neutrophils. The blood Kahn reaction was negative. The nonprotein nitrogen was 159 mg, the creatinine 60 mg, the total protein 7.4 gm, and the blood chloride (as sodium chloride) 430 mg per 100 cc.

A gastrointestinal series showed an irregular duodenal cap and moderate pyloric obstruction to the passage of barium. Intravenous pyelograms disclosed no visible excretion of the diodrast. An intravenous phenolsulfonephthalein excretion test revealed a total of 10 per cent excretion of the dye in 2 hours. A urine concentration test demonstrated a maximum specific gravity of 1.010. Fifteen routine morning urine specimens showed specific gravities ranging from 1.003 to 1.012. In one specimen the sediment contained rare red cells, and in several it contained from 1 to 8 white cells per centrifuged high-power field. At no time was albumin or casts observed.

After admission the patient showed no signs of gastrointestinal bleeding. He was placed on hourly administration of milk and cream and antacids. Vomiting, however, became severe, and constant suction was begun through a Levine tube introduced into the stomach. Large quantities of dextrose and saline solutions, 1500 cc. of plasma and 500 cc. of whole blood were administered intravenously during the first 2 hospital weeks. The suction was discontinued at the end of 5 days, and vomiting did not immediately recur. About 2 weeks after admission the blood pressure was 130/72, and the nonprotein nitrogen had fallen to 60 mg and the blood creatinine to 3.2 mg per 100 cc. The white-cell count was 5800, and the hemoglobin 8.7 gm. The patient remained relatively asymptomatic and gained about 10 pounds of weight during the ensuing month. During this time he began taking about 15 gm of sodium bicarbonate daily for relief of mild epigastric distress.

Two months after admission he experienced more severe epigastric pain and repeated vomiting. He became extremely weak, the pulse became rapid, and the blood pressure fell to 80/60. He lost 12 pounds of weight in 1 week. The nonprotein nitrogen rose to 100 mg, and the creatinine to 7.5 mg per 100 cc. The blood chloride (as sodium chloride) was 429 mg per 100 cc. At this time the patient was seen by several medical consultants. The presence of diffuse tanning of the skin, nausea and vomiting, elevation of nonprotein nitrogen and creatinine, marked asthenia and weight loss led to a diagnosis of Addison's disease in crisis. The absence of known hypertension and of albumin and formed elements in the urine, the normal heart size and the normal eye grounds were all taken as indications that the patient did not have a significant degree of nephritis. Part I of the water diuresis test of Robinson, Power and Kepler² was performed and interpreted as being consistent with the diagnosis of Addison's disease. The night urinary volume was 1715 cc, and the maximum hourly urine specimen after the ingestion of water was 200 cc.

In view of the diagnosis of Addison's disease the patient was given 36 gm of sodium chloride and 30 cc of adrenocortical extract intravenously on May 21 and 22, and was started on desoxycorticosterone acetate in oil (DOCA) intramuscularly, 10 mg a day. He continued to receive 15 gm of sodium bicarbonate by mouth daily. The immediate response was dramatic (Fig 1), the blood pressure rose in 3 days to 110/68, and the patient experienced marked subjective improvement. This was interpreted as added evidence for the presence of Addison's disease. Despite the continuation of 10 mg of DOCA daily, however, as well as the 15 gm of sodium bicarbonate, the symptoms of asthenia, nausea and vomiting returned. Over the course of 10 days

*From the Medical Service, Veterans Administration Hospital, Togus, Maine.

†Formerly assigned by United States Navy to Medical Service, Veterans Administration Hospital, Togus, Maine.

‡Assistant resident, Medical Service, Veterans Administration Hospital, Batavia, New York, formerly assigned by United States Army to Medical Service, Veterans Administration Hospital, Togus, Maine.

the blood pressure again fell to 80/50. He was again treated with 20 cc of adrenocortical extract and 18 gm of sodium chloride given intravenously. He was also placed on 5 gm of sodium chloride in enteric-coated capsules daily in addition to the dietary salt and 15 gm of sodium bicarbonate orally. On this regime there was again a definite subjective improvement, and the blood pressure and body weight showed a more gradual but definite rise (Fig 1).

At this point it was suspected that the patient had a salt-losing nephritis as described by Thorn, Koepf and Clinton.¹ Accordingly, on June 17, DOCA was discontinued. The

the same amounts of salt and bicarbonate, to watch for the formation of edema, and to follow an intermediate ulcer diet. The diagnoses on discharge were salt-losing nephritis and duodenal ulcer, chronic, with partial obstruction.

He adjusted himself well at home on this regime but did not return to work. He followed the directions until about 4 months after discharge, when he again experienced epigastric pain and vomiting. He re-entered this hospital on December 9, after a 3-day period of hematemesis and melena. On admission he appeared very pale and weak. The body weight was 128 pounds. The blood urea nitrogen was only 37 mg, the

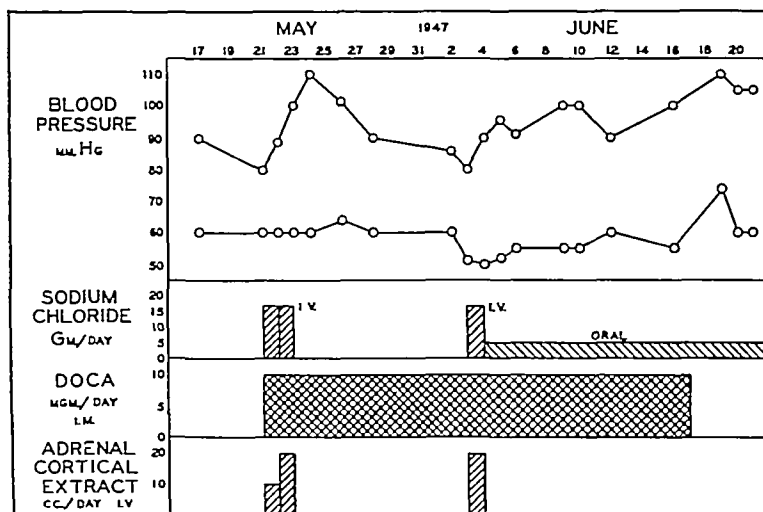


FIGURE 1 Ineffectiveness of Desoxycorticosterone Acetate in Oil (DOCA), 10 mg Intramuscularly Daily, in Maintaining the Blood Pressure of a Patient with Salt-Losing Nephritis

patient continued to show a steady rise in blood pressure, body weight and feeling of well-being on sodium chloride and sodium bicarbonate given orally alone.

Since a patient with adrenal insufficiency alone might show similar improvement on this therapy, an attempt was made to determine whether the kidney itself was unable to respond to the administration of DOCA. Urinary and blood chloride determinations, blood pressure and body weight were followed before, during and after the administration of a large daily dose (20 mg) of DOCA for 7 days. The diet was kept constant during this period, and the patient continued to take 5 gm of sodium chloride and 15 gm of sodium bicarbonate orally. The results obtained are shown diagrammatically in Fig 2. It appears that gains in body weight and blood pressure during this observation period, including the time before and after DOCA was administered, were quite steady and not greatly influenced by the administration of the drug. There was only a slight decrease in the concentration of urinary chloride from 650 to 600 mg per 100 cc (as sodium chloride) during the administration of DOCA, and the blood chloride level was not greatly altered.

A pituitrin concentration test, consisting of 10 units of pituitrin given subcutaneously, was performed, and the urine collected at one and two hours. The specific gravities of the specimens were 1.009 and 1.008 respectively. An intravenous glucose tolerance test was also performed, 0.5 gm of glucose per kilogram of body weight being given intravenously over a 30-minute period. Blood glucose levels were as follows: fasting control 111 mg, 1 hour 167 mg, 2 hours 114 mg, 3 hours 87 mg, and 4 hours 83 mg per 100 cc.

The patient continued to feel well on 5 gm of salt and 15 gm of sodium bicarbonate by mouth daily. The blood urea nitrogen was relatively stable at between 35 and 45 mg per 100 cc. The carbon dioxide combining power ranged between 55 and 65 vol per cent. The weight reached 127 pounds. He was discharged on August 23, with advice to continue taking

creatinine 2.7 mg, and the blood chloride (as sodium chloride) 483 mg per 100 cc. The urinary specific gravity was 1.007, and no formed elements or albumin was present. Repeated blood transfusions were given, but signs of slow bleeding continued. On December 26 a subtotal gastrectomy was performed as an emergency procedure. After operation the patient developed clinical and roentgenologic signs of pulmonary edema. The blood nonprotein nitrogen was 150 mg per 100 cc, and the red-cell count 4,200,000. Despite oxygen, morphine, digitoxin and penicillin the signs of pulmonary congestion increased, and early on the morning of December 28, he had a single clonic convulsion and died.

At autopsy* there was a fresh midline upper abdominal scar. The skin was a diffuse light brown.

The pleural cavities contained about 550 cc of pink fluid. The peritoneal cavity contained 100 cc of red fluid. There was a recent gastric resection, and gastrojejunostomy. These anastomoses were firm and healing in good position. The duodenal stump was closed and covered with omentum.

The right lung weighed 1100 and the left 850 gm. They were firm and boggy in consistence. On section there was a tremendous amount of foamy pink fluid from all lobes and in the major bronchi.

The heart weighed 380 gm. There was dilatation of the right ventricle, and the coronary arteries were extensively calcified. There was moderate narrowing, but no occlusion of the vessels.

There were two ulcers in the duodenal stump. The remainder of the intestinal tract was normal except for large amounts of black fecal matter.

The liver weighed 2050 and the spleen 300 gm. Both showed chronic passive congestion.

The pancreas weighed 100 gm, the head was firm, and the body and tail were normal in color and consistence.

*Performed by Dr. Russell H. Pope.

The adrenal glands were greatly increased in size. The left weighed 21 gm. The right was torn during removal and could not be weighed but appeared similar in size to the left. The cortex was normal in color and about twice the normal width.

The kidneys were small, weighing 70 gm each. The capsules stripped with difficulty. The surface was finely granular. The organs cut with increased resistance to the knife. The cortex was reduced in width, being about 3 mm thick. The boundaries between cortex and medulla were indistinct. The pyramids were small but not flattened. The pelvic mucosa

appreciable intimal disease. There were numerous cystic spaces surrounded by a heavy layer of pink-staining acellular material containing a blue-staining substance resembling calcium. These were located for the most part in the connective-tissue septums.

The kidneys, on multiple sections, demonstrated remarkably few functioning glomeruli. Nearly all were represented by hyaline balls, some of which showed blue-staining calcific precipitates. Occasional glomeruli appeared to be functioning, but even these revealed separation of the tufts, adhesions and marked thickening of Bowman's capsule. A

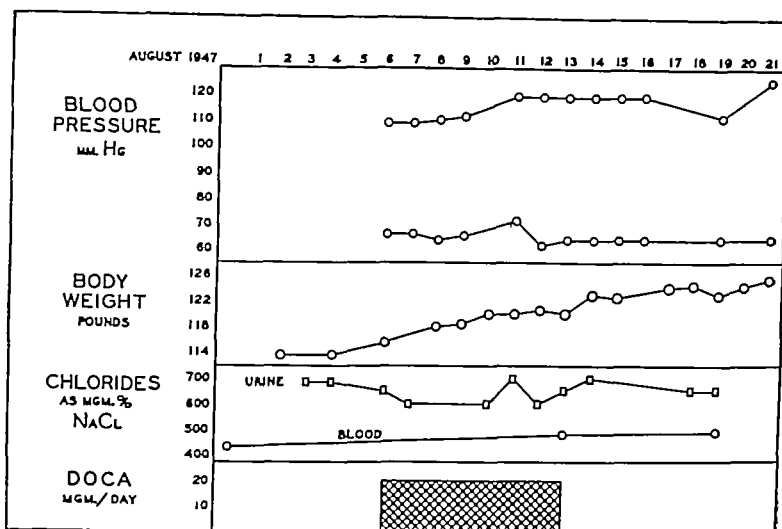


FIGURE 2 Ineffectiveness of Desoxycorticosterone Acetate in Oil (DOCA), 20 mg Intramuscularly Daily, in Significantly Altering the Blood Pressure, Body Weight and Urinary Excretion of Chloride in a Patient with Salt-Losing Nephritis

was smooth and white except for a few small petechial hemorrhages. The ureters, bladder and prostate appeared normal. The thyroid and parathyroid glands, brain and spinal cord were not examined.

Microscopical examination of the lungs showed moderate dilatation of the alveoli. The alveolar septums were thickened in many areas, with definitely increased connective tissue. The ends of the septums were clubbed and contained round, dark-blue granules surrounded by dark-blue rings suggestive of calcium. Streaks of granular, dark-blue material were seen along some of the septums. Near the hilar region these granules were quite numerous and in places had been shed into the alveolar spaces. In these areas the alveolar walls appeared quite stiff and thickened, and calcific rings were apparent in the septums, sometimes surrounding an entire alveolus. Some of the smaller vessels showed extensive calcific deposits in the media. A rare foreign-body giant cell was seen surrounding the calcific granules. Many of the alveoli were filled with protein precipitates and comprised many large macrophages containing dark pigment. The vessels of the lung were greatly dilated.

The heart revealed definite hypertrophy of the muscle fibers, the interstitial spaces appeared swollen and vacuolated. The smaller arteries demonstrated slight calcific changes in the media. There were early calcific deposits at the base of the aortic valve. The coronary arteries showed only slight fibrous thickening of the intima without cholesterol deposits. The media just below the internal elastic membrane was completely replaced in a ring-like manner by heavy deposits of calcium, which were strictly limited to the media. This calcification extended from the ostia into the smallest arterioles.

The liver and spleen disclosed chronic passive congestion. The larger vessels running through the parenchyma of the pancreas showed marked medial calcification without

few disclosed partial hyalinization. The renal parenchyma was greatly altered by an increase in connective tissue and areas of round cells. Many of the tubules were atrophied, and the epithelial cells were small, clumped together and surrounded by a remarkably thickened basement membrane. In a few places this membrane took a dark-blue stain suggesting calcium. The calcification of the basement membrane was quite striking and was seen on all the sections. There were extensive calcium deposits of another type in every field. These consisted of a great number of dark-staining granules clumped together to form irregular masses. The pyramids were extensively calcified in this manner, and some of the hypertrophied tubules were filled with these calcific balls but for the most part they seemed to be in the interstitial spaces. The larger arteries showed a severe degree of medial calcification. The veins were distended. The entire parenchyma was much reduced in width. The pelvic and ureteral epithelium was normal.

The adrenal glands demonstrated a diffuse increase in the cortical area and several small hyperplastic nodules or adenomas. The cortex appeared twice as thick as normal. The medullary cells were normal except for moderate atrophy.

Sections of bone taken from the sternum revealed no noticeable changes in the bony trabeculae or marrow.

DISCUSSION

The post-mortem studies corroborated the diagnoses of chronic duodenal ulcer and renal disease without Addison's disease. The most interesting findings were the extensive deposits of calcium in the lungs, kidneys and pancreas and in

the media of the arteries, including the coronary arteries. The medial calcification could not be considered ordinary arteriosclerosis because of the definite lack of intimal changes in the larger arteries. It seemed to be a special form of calcification resembling Mönckeberg's sclerosis or senile arteriosclerosis. It has been described as due to calcinosis from various causes. The calcification in this case was not extensive enough to be considered calcinosis but falls into the group of cases with "metastatic calcification."³ Most of these patients were emaciated with severe disease of the bones, but the patient in the case reported above had no bone disease. Similar lesions can be produced in animals with excessive doses of vitamin D, chronic alkalosis and hypochloremia.⁴ The calcification of the tubular basement membrane in this case suggested a specific disease of the tubules in view of the presence of salt-losing nephritis. The extensive deposits of calcium in other tissues pointed to a more general metabolic dyscrasia. The cause of this was open to speculation. This dyscrasia may have been associated with the large amount of alkali consumed by the patient over a long period. The interstitial calcification of the kidneys is a common finding in chronic renal disease and undoubtedly resulted, at least in part, from local increased alkalinity of the renal tissues.

The cause of death was probably pulmonary edema and cardiac edema and dilatation due to an overloaded circulation following multiple transfusions for the shock of operation and the prolonged gastrointestinal hemorrhage.

This case bore a striking resemblance in many respects to the 2 reported by Thorn, Koepf and Clinton.¹ Only once during the last two periods of hospitalization did the patient show abnormal formed elements in the urine, and examination never disclosed albuminuria. Formed elements were notably absent in the urine in both the cases reported by Thorn, Koepf and Clinton. Other findings in common were hypotension, normal heart size, normal eye grounds, weight loss, nausea and vomiting. A slight or absent response to DOCA and a satisfactory response to salt alone were also striking in these cases. The age of the patient, however, was fifty-three when first seen here. Both patients of Thorn et al. were twenty-one at the time of onset.

Both their patients entered a terminal stage consisting of edema, hypertension, nitrogen retention and cardiac failure. Death in the case presented above was precipitated by acute severe gastrointestinal hemorrhage, the emergency operation and multiple transfusions. Pulmonary edema appeared and was probably responsible for death. This terminal picture was not allowed to develop naturally as in the 2 cases of Thorn et al.

Our case was complicated by the presence of chronic duodenal obstruction. This undoubtedly

contributed greatly to the salt loss, particularly the chloride loss. During one period of severe protracted vomiting and hypotension, however, the patient maintained a daily urinary chloride excretion of over 18 gm (as sodium chloride) and a daily urine volume of over 3 liters. This should have demonstrated that his kidneys were unable to retain chlorides and water at a time when they were most desperately needed to maintain the chemical equilibrium. A similar picture may be seen in adrenal insufficiency when there is moderate salt loss from vomiting, diarrhea, fever or excessive sweating. Here again the kidneys are unable to retain salt in the absence of adrenocortical hormones, the electrolyte balance suffers, and Addisonian crisis may ensue.⁵

The pathological picture of the kidneys in the cases reported by Thorn, Koepf and Clinton¹ could not be called specific. The authors concluded that salt-losing nephritis occurred late in the course of slowly progressive kidney disease. Their cases showed extensive scarring, hypertrophy of the remaining glomeruli, and dilatation of the tubules.¹ The findings in the kidneys in our case were consistent with a severe chronic glomerulonephritis, and nothing that could be interpreted as being a specific tubular lesion was demonstrated.

Instead of atrophy or absence of the adrenal glands, autopsy revealed a fairly marked hyperplasia of the adrenal cortex. It is of interest to note that 1 case of Thorn, Koepf and Clinton also showed definite hypertrophy of the adrenal cortex, although the authors did not comment on this fact. One may speculate that since hypertrophy of the adrenal cortex was present in 2 out of 3 reported cases of salt-losing nephritis the cause of such hypertrophy is the salt loss itself. Such hypertrophy may represent an attempt on the part of the adrenal cortex to stimulate the renal tubules to retain salt and compensate for the excessive salt loss.

It is not known whether a low blood sodium or chloride can stimulate the adrenal cortex.⁶ There were undoubtedly other adequate causes for adrenal hypertrophy in this case, but this remains a possibility. A rough parallel might be drawn between such a hypothetical mechanism and the known mechanism of parathyroid hypertrophy in cases in which there is an excessive loss of calcium ion in the urine. Albright et al.⁷ have shown that the stimulus to parathyroid hypertrophy in such cases is the depression of blood calcium concentration.

In chronic renal insufficiency significant salt loss is not rare.^{8,9} Its recognition may be very important in cases that show neither edema nor hypertension. When such salt loss exists it contributes to the retention of nitrogenous substances in the blood. The depletion of salt in the body fluids decreases the rate of glomerular filtration probably by reducing the renal blood flow.¹⁰ In such cases the salt loss may be easily replaced by the cautious

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appreciable intimal disease. There were numerous cystic spaces surrounded by a heavy layer of pink-staining acellular material containing a blue-staining substance resembling calcium. These were located for the most part in the connective-tissue septums.

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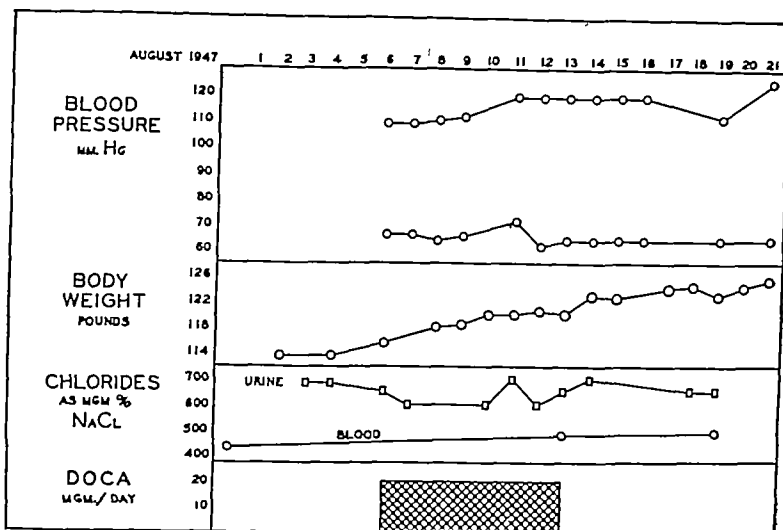


FIGURE 2 Ineffectiveness of Desoxycorticosterone Acetate in Oil (DOCA), 20 mg Intramuscularly Daily, in Significantly Altering the Blood Pressure, Body Weight and Urinary Excretion of Chloride in a Patient with Salt-Losing Nephritis

was smooth and white except for a few small petechial hemorrhages. The ureters, bladder and prostate appeared normal.

The thyroid and parathyroid glands, brain and spinal cord were not examined.

Microscopical examination of the lungs showed moderate dilatation of the alveoli. The alveolar septums were thickened in many areas, with definitely increased connective tissue. The ends of the septums were clubbed and contained round, dark-blue granules surrounded by dark-blue rings suggestive of calcium. Streaks of granular, dark-blue material were seen along some of the septums. Near the hilar region these granules were quite numerous and in places had been shed into the alveolar spaces. In these areas the alveolar walls appeared quite stiff and thickened, and calcific rings were apparent in the septums, sometimes surrounding an entire alveolus. Some of the smaller vessels showed extensive calcific deposits in the media. A rare foreign-body giant cell was seen surrounding the calcific granules. Many of the alveoli were filled with protein precipitates and comprised many large macrophages containing dark pigment. The vessels of the lung were greatly dilated.

The heart revealed definite hypertrophy of the muscle fibers, the interstitial spaces appeared swollen and vacuolated. The smaller arteries demonstrated slight calcific changes in the media. There were early calcific deposits at the base of the aortic valve. The coronary arteries showed only slight fibrous thickening of the intima without cholesterol deposits. The media just below the internal elastic membrane was completely replaced in a ring-like manner by heavy deposits of calcium, which were strictly limited to the media. This calcification extended from the ostia into the smallest arterioles.

The liver and spleen disclosed chronic passive congestion. The larger vessels running through the parenchyma of the pancreas showed marked medial calcification without

few disclosed partial hyalinization. The renal parenchyma was greatly altered by an increase in connective tissue and areas of round cells. Many of the tubules were atrophied, and the epithelial cells were small, clumped together and surrounded by a remarkably thickened basement membrane. In a few places this membrane took a dark-blue stain suggesting calcium. The calcification of the basement membrane was quite striking and was seen on all the sections. There were extensive calcium deposits of another type in every field. These consisted of a great number of dark-staining granules clumped together to form irregular masses. The pyramids were extensively calcified in this manner, and some of the hypertrophied tubules were filled with these calcific balls but for the most part they seemed to be in the interstitial spaces. The larger arteries showed a severe degree of medial calcification. The veins were distended. The entire parenchyma was much reduced in width. The pelvic and ureteral epithelium was normal.

The adrenal glands demonstrated a diffuse increase in the cortical area and several small hyperplastic nodules or adenomas. The cortex appeared twice as thick as normal. The medullary cells were normal except for moderate autolysis.

Sections of bone taken from the sternum revealed no noticeable changes in the bony trabeculae or marrow.

Discussion

The post-mortem studies corroborated the diagnoses of chronic duodenal ulcer and renal disease without Addison's disease. The most interesting findings were the extensive deposits of calcium in the lungs, kidneys and pancreas and in

the media of the arteries, including the coronary arteries. The medial calcification could not be considered ordinary arteriosclerosis because of the definite lack of intimal changes in the larger arteries. It seemed to be a special form of calcification resembling Mönckeberg's sclerosis or senile arteriosclerosis. It has been described as due to calcinosis from various causes. The calcification in this case was not extensive enough to be considered calcinosis but falls into the group of cases with "metastatic calcification."³ Most of these patients were emaciated with severe disease of the bones, but the patient in the case reported above had no bone disease. Similar lesions can be produced in animals with excessive doses of vitamin D, chronic alkalosis and hypochloremia.⁴ The calcification of the tubular basement membrane in this case suggested a specific disease of the tubules in view of the presence of salt-losing nephritis. The extensive deposits of calcium in other tissues pointed to a more general metabolic dyscrasia. The cause of this was open to speculation. This dyscrasia may have been associated with the large amount of alkali consumed by the patient over a long period. The interstitial calcification of the kidneys is a common finding in chronic renal disease and undoubtedly resulted, at least in part, from local increased alkalinity of the renal tissues.

The cause of death was probably pulmonary edema and cardiac edema and dilatation due to an overloaded circulation following multiple transfusions for the shock of operation and the prolonged gastrointestinal hemorrhage.

This case bore a striking resemblance in many respects to the 2 reported by Thorn, Koepf and Clinton.¹ Only once during the last two periods of hospitalization did the patient show abnormal formed elements in the urine, and examination never disclosed albuminuria. Formed elements were notably absent in the urine in both the cases reported by Thorn, Koepf and Clinton. Other findings in common were hypotension, normal heart size, normal eye grounds, weight loss, nausea and vomiting. A slight or absent response to DOCA and a satisfactory response to salt alone were also striking in these cases. The age of the patient, however, was fifty-three when first seen here. Both patients of Thorn et al. were twenty-one at the time of onset.

Both their patients entered a terminal stage consisting of edema, hypertension, nitrogen retention and cardiac failure. Death in the case presented above was precipitated by acute severe gastrointestinal hemorrhage, the emergency operation and multiple transfusions. Pulmonary edema appeared and was probably responsible for death. This terminal picture was not allowed to develop naturally as in the 2 cases of Thorn et al.

Our case was complicated by the presence of chronic duodenal obstruction. This undoubtedly

contributed greatly to the salt loss, particularly the chloride loss. During one period of severe protracted vomiting and hypotension, however, the patient maintained a daily urinary chloride excretion of over 18 gm (as sodium chloride) and a daily urine volume of over 3 liters. This should have demonstrated that his kidneys were unable to retain chlorides and water at a time when they were most desperately needed to maintain the chemical equilibrium. A similar picture may be seen in adrenal insufficiency when there is moderate salt loss from vomiting, diarrhea, fever or excessive sweating. Here again the kidneys are unable to retain salt in the absence of adrenocortical hormones, the electrolyte balance suffers, and Addisonian crisis may ensue.⁵

The pathological picture of the kidneys in the cases reported by Thorn, Koepf and Clinton¹ could not be called specific. The authors concluded that salt-losing nephritis occurred late in the course of slowly progressive kidney disease. Their cases showed extensive scarring, hypertrophy of the remaining glomeruli, and dilatation of the tubules.¹ The findings in the kidneys in our case were consistent with a severe chronic glomerulonephritis, and nothing that could be interpreted as being a specific tubular lesion was demonstrated.

Instead of atrophy or absence of the adrenal glands, autopsy revealed a fairly marked hyperplasia of the adrenal cortex. It is of interest to note that 1 case of Thorn, Koepf and Clinton also showed definite hypertrophy of the adrenal cortex, although the authors did not comment on this fact. One may speculate that since hypertrophy of the adrenal cortex was present in 2 out of 3 reported cases of salt-losing nephritis the cause of such hypertrophy is the salt loss itself. Such hypertrophy may represent an attempt on the part of the adrenal cortex to stimulate the renal tubules to retain salt and compensate for the excessive salt loss.

It is not known whether a low blood sodium or chloride can stimulate the adrenal cortex.⁶ There were undoubtedly other adequate causes for adrenal hypertrophy in this case, but this remains a possibility. A rough parallel might be drawn between such a hypothetical mechanism and the known mechanism of parathyroid hypertrophy in cases in which there is an excessive loss of calcium ion in the urine. Albright et al.⁷ have shown that the stimulus to parathyroid hypertrophy in such cases is the depression of blood calcium concentration.

In chronic renal insufficiency significant salt loss is not rare.^{8,9} Its recognition may be very important in cases that show neither edema nor hypertension. When such salt loss exists it contributes to the retention of nitrogenous substances in the blood. The depletion of salt in the body fluids decreases the rate of glomerular filtration probably by reducing the renal blood flow.¹⁰ In such cases the salt loss may be easily replaced by the cautious

The adrenal glands were greatly increased in size. The left weighed 21 gm. The right was torn during removal and could not be weighed but appeared similar in size to the left. The cortex was normal in color and about twice the normal width.

The kidneys were small, weighing 70 gm each. The capsules stripped with difficulty. The surface was finely granular. The organs cut with increased resistance to the knife. The cortex was reduced in width, being about 3 mm thick. The boundaries between cortex and medulla were indistinct. The pyramids were small but not flattened. The pelvic mucosa

appreciable intimal disease. There were numerous cystic spaces surrounded by a heavy layer of pink-staining acellular material containing a blue-staining substance resembling calcium. These were located for the most part in the connective-tissue septums.

The kidneys, on multiple sections, demonstrated remarkably few functioning glomeruli. Nearly all were represented by hyaline balls, some of which showed blue staining calcific precipitates. Occasional glomeruli appeared to be functioning, but even these revealed separation of the tuft, adhesions and marked thickening of Bowman's capsule.

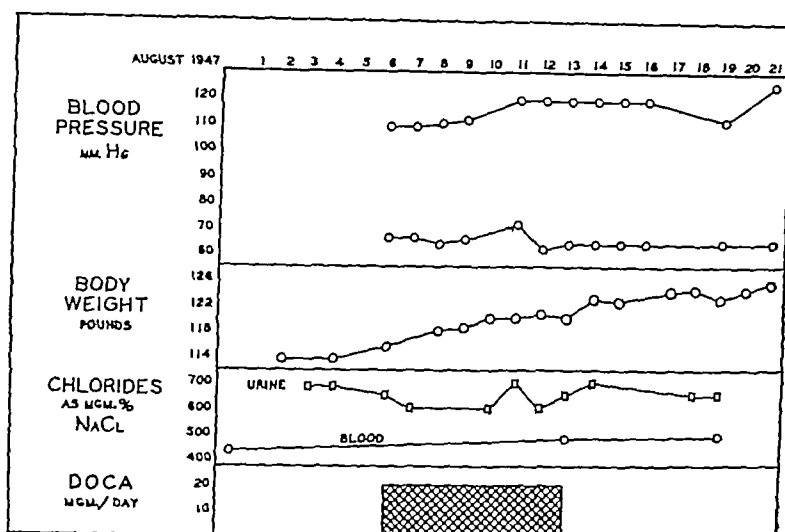


FIGURE 2 Ineffectiveness of Desoxycorticosterone Acetate in Oil (DOCA), 20 mg Intramuscularly Daily, in Significantly Altering the Blood Pressure, Body Weight and Urinary Excretion of Chloride in a Patient with Salt-Losing Nephritis

was smooth and white except for a few small petechial hemorrhages. The ureters, bladder and prostate appeared normal.

The thyroid and parathyroid glands, brain and spinal cord were not examined.

Microscopical examination of the lungs showed moderate dilatation of the alveoli. The alveolar septums were thickened in many areas, with definitely increased connective tissue. The ends of the septums were clubbed and contained round, dark-blue granules surrounded by dark-blue rings suggestive of calcium. Streaks of granular, dark-blue material were seen along some of the septums. Near the hilar region these granules were quite numerous and in places had been shed into the alveolar spaces. In these areas the alveolar walls appeared quite stiff and thickened, and calcific rings were apparent in the septums, sometimes surrounding an entire alveolus. Some of the smaller vessels showed extensive calcific deposits in the media. A rare foreign-body giant cell was seen surrounding the calcific granules. Many of the alveoli were filled with protein precipitates and comprised many large macrophages containing dark pigment. The vessels of the lung were greatly dilated.

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addition of extra salt to the diet. This in turn produces a decrease in nitrogen retention. Since the concentration of salt in the urine may be relatively fixed, variation in the urinary volume causes a proportional variation in the total salt excretion. Thus, forcing of fluids may make the salt loss more marked unless additional salt intake compensates for this loss.⁸

Salt loss of sufficient magnitude to cause symptoms simulating adrenocortical insufficiency, however, is probably quite rare.¹ It is important that it be recognized since the response to added sodium chloride and bicarbonate may be quite gratifying. Even with a reasonable suspicion of the presence of such a condition it may be very difficult to rule out the possibility of a combination of both renal and adrenocortical insufficiencies. This can best be illustrated by our experience in the case presented above. Many procedures of use in the diagnosis of Addison's disease were unreliable in the presence of advanced renal insufficiency of this type.

Hypoglycemia is common in Addison's disease and should not be influenced by renal failure. Our patient had no hypoglycemia and had a relatively normal intravenous glucose tolerance test. This indicates that there was no profound disturbance of carbohydrate metabolism and that normal adrenal glands were present.

Urea and creatinine retention decreased by the administration of salt may occur in either adrenal or renal insufficiency. The high degree of retention and its persistence despite vigorous therapy were strong indications that a considerable degree of renal insufficiency was present.

The water diuresis test² was positive for Addison's disease in our case. This was to be expected since this test depends on the ability of the kidney to vary the volume of urine and to excrete urea and retain chloride. The functions of the kidney may be impaired in both conditions, and this test was of little or no value in distinguishing this type of renal failure from Addison's disease.^{11, 12} A salt-deprivation test¹³ might also be expected to yield a positive result in the presence of marked renal salt loss.

Urinary 17-ketosteroid excretion¹⁴ or the urinary output of cortical hormones¹⁵ should be reduced in adrenocortical insufficiency. A low urinary excretion of 17-ketosteroids would have been of little help in itself. This may occur in chronic debilitating diseases even in the presence of anatomically normal adrenal glands.¹⁶ This was true in 1 of the cases of salt-losing nephritis reported by Thorn, Koepf and Clinton.¹ If a normal value had been found in our case it would have been of great help in establishing the proper diagnosis. Unfortunately, laboratory facilities for such assays were not immediately available to us.

Also valuable would have been the determination of eosinophile response to the pituitary adrenocorticotrophic hormone.¹⁷ A normal fall in eosinophil count following the administration of this hormone would have been strong evidence for the presence of an intact adrenal cortex. The necessary material, however, was not available to us.

Of prime importance in the establishment of the renal basis for the excessive salt loss in this patient was the lack of a normal response to the administration of DOCA. We observed that large daily doses of the drug did not maintain the patient (Fig. 1) or substantially alter the concentration of chloride in the urine, the blood pressure or the body weight (Fig. 2). Such doses of DOCA should exert a striking effect on the reabsorption of sodium and chloride by the intact renal tubule. In a patient with normal kidneys, with or without normal adrenocortical function, this should manifest itself by a marked reduction in the renal excretion of chloride.^{18, 19}

The loss of salt in this type of renal insufficiency may be compared to the more common loss of water. Polyuria, with the excretion of large volumes of urine of low specific gravity, is a frequent symptom of renal insufficiency. This probably represents in part an inability of the renal tubules to reabsorb normal amounts of water. In these respects it resembles the polyuria of diabetes insipidus. Such polyuria, however, is not influenced by the injection of large amounts of the antidiuretic hormone of the pituitary body. It thus represents disease of the end-organ, the renal tubule, simulating disease of the posterior lobe. In salt-losing nephritis the diseased tubule is unable to respond to the influence of DOCA or natural adrenocortical hormones. This again is disease of the same end-organ simulating disease of another endocrine organ—in this case, the adrenal cortex.

Manifestations of the tubular inability to reabsorb water as well as salt were present in our case. Polyuria with the excretion of over 3 liters a day of urine of low specific gravity persisted even during periods of severe dehydration. The specific gravity did not rise after the administration of pituitrin.

This case is presented to point out at least one condition in which *excessive loss* of vital substance in the urine was of primary clinical importance in renal insufficiency. It is more usual to think of renal failure in terms of *retention* of nitrogenous products, electrolytes and water. It is important to recognize the stages of renal insufficiency in which the loss of ability to reabsorb a given solute is significant. The substances that may be lost to an important degree in renal diseases are water, sodium, chloride,^{8, 9} calcium,⁷ phosphate, amino acids and glucose.²⁰ Recognition of any such loss makes replacement therapy possible and may lead to the partial rehabilitation of the patient. This was well illustrated by our case, in which compen-

sation for the excessive urinary loss of sodium and chloride led to at least temporary relief from the most pressing symptoms

SUMMARY

A case of salt-losing nephritis simulating adrenocortical insufficiency, with the pathological findings, is presented

The difficulties of differential diagnosis and the importance of recognition and proper treatment are discussed

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TRIMETON, A NEW ANTIHISTAMINIC DRUG*

A Clinical Evaluation

IRVING W. SCHILLER, M.D.,† AND FRANCIS C. LOWELL, M.D.‡

BOSTON

THOUGH the evidence is still very indirect that histamine is responsible for the allergic reaction,^{1, 2} the effectiveness of the antihistaminic drugs in the symptomatic control of hay fever, urticaria and certain cases of perennial allergic rhinitis is well recognized. On the other hand, the value of these drugs in bronchial asthma, allergic dermatoses and drug allergy is questionable. The reason for lack of benefit in these conditions is not clear. The experience with pyribenzamine ointment in the treatment of skin conditions suggests that higher concentrations at the involved site are an important factor. Furthermore, in studies in this laboratory, it has been found that whereas small doses of pyribenzamine injected intravenously may have negligible influence on induced asthmatic attacks,³ much larger doses often give short-lived protection.⁴ These experiments employing larger

doses are limited, however, by undesirable side reactions. Also, recent studies have called attention to certain other pharmacologic effects of these drugs,⁵ not specifically referable to histamine antagonism. It appears, therefore, that a search for highly specific antihistamines with low toxicity is well warranted. In an effort to obtain these agents, a number of new synthetic compounds have been offered for clinical trial, among which are the substituted pyridylalkylaminoalkanes. One of these compounds, 1-phenyl-1-(2-pyridyl)-3-dimethylaminopropane (trimeton),§ has been shown in animal experiments to possess a high degree of antihistaminic activity and low toxicity.^{6, 7} Its structural formula is shown in Figure 1. The purpose of this paper is to report on the efficacy of this drug in certain allergic disorders.

Trimeton tablets for oral administration were given to 84 allergic patients ranging in age from five to sixty years. These patients, who were about equally divided with respect to sex, had received serial injections of allergenic extracts, and offending allergens had been eliminated so far as possible

*From the Allergy Clinic, Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.

†Instructor in medicine, Boston University School of Medicine, assistant physician, Allergy Clinic, Massachusetts Memorial Hospitals.

‡Associate professor of medicine, Boston University School of Medicine, staff member, Robert Dawson Evans Memorial, and physician in-charge, Allergy Clinic, Massachusetts Memorial Hospitals.

§Kindly supplied by the Schering Corporation, Bloomfield, New Jersey.

All patients were exhibiting symptoms at the time trimeton therapy was instituted. The drug was given in doses of 25 mg to 125 mg a day, and all patients were observed for several weeks and instructed to report in detail all subjective symptoms. In some cases, placebo controls were used. Relief of symptoms, when it occurred, was usually noted thirty minutes after a tablet was taken, and relief often lasted, with certain exceptions, for three or

ness. The side effects were chiefly drowsiness (6 cases, or 7 per cent) and dryness of the mouth (3 cases, or 3 per cent). Nervousness, restlessness, nausea, dizziness or diarrhea was not noted, and weakness occurred in only 1 case (1 per cent).

DISCUSSION

From these limited clinical observations, trimeton appears to be highly satisfactory in the symptomatic treatment of hay fever, urticaria and perennial allergic rhinitis. Trimeton compared favorably with pyribenzamine and benadryl in all respects and is distinctly superior to them in its effect in perennial allergic rhinitis. Experience in this clinic with the latter compounds in the treatment of perennial allergic rhinitis has been disappointing and not in accord with the reports of other investigators. In a number of cases we had the opportunity of prescribing trimeton after pyribenzamine and benadryl had failed to give relief, and frequently trimeton was strikingly effective. In the 55 cases of perennial allergic rhinitis treated with trimeton, there were only 8 (14 per cent) who obtained no relief. Though the number of cases studied was small and treatment with allergenic extracts had been given, the figure of 85 per cent satisfactorily treated patients is impressive.

Trimeton was particularly valuable for its low incidence of side reactions. These were mild and were experienced by only 11 per cent of the patients. Dryness of the mouth and drowsiness were the chief side effects, and such reactions as restlessness, nervousness, nausea and dizziness, found in some of the other commonly employed antihistaminic drugs, were notably absent.

SUMMARY

Trimeton, a new antihistaminic drug, was clinically evaluated in 84 patients with hay fever, urticaria and perennial allergic rhinitis. Because of the favorable therapeutic response, the drug gives promise of being a valuable addition to the growing group of histamine-antagonizing compounds.

Trimeton compares favorably with pyribenzamine and benadryl in the management of certain allergic conditions and appears to be particularly effective in the symptomatic treatment of perennial allergic rhinitis.

The side reactions, occurring in only 10 of 84 patients, were mild.

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TRIMETON

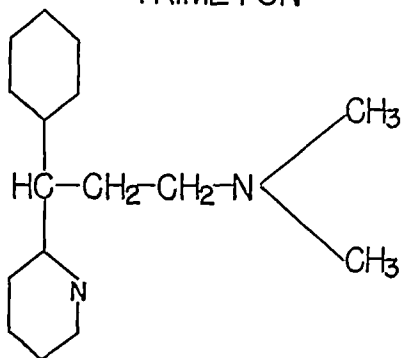


FIGURE 1 Structural Formula of Trimeton

more hours. Withdrawal of the drug was usually followed by a return of the symptoms.

Table 1 presents the results. Twelve patients with urticaria reported satisfactory relief of symptoms. Of 55 patients with perennial allergic rhinitis 47 (85 per cent) reported satisfactory or partial relief. Three of these patients were recorded as having obtained partial relief but actually were benefited satisfactorily for "about half an hour." Increasing the dose of the drug in these cases seemed to make very little difference in prolonging relief. Of 15 patients with hay fever 13 (86 per cent) reported satisfactory or partial relief. One patient

TABLE 1 Therapeutic Response to Trimeton

DIAGNOSIS	TOTAL CASES	SATISFACTORY RELIEF NO OF CASES	PARTIAL RELIEF NO OF CASES	NO RELIEF NO OF CASES
Hay fever	15	10	3	2
Allergic rhinitis, perennial	55	33	14	8
Urticaria	12	12	—	—
Vernal catarrh	1	—	—	1
Atopic dermatitis	1	—	—	1
Totals	84	55	17	12

with vernal catarrh who had many positive reactions to pollens and a patient with atopic dermatitis failed to obtain symptomatic relief.

Of the 84 patients, 74 (88 per cent) were completely free from any undesirable side reactions. The reactions noted in the remaining 10 (11 per cent) were mild, and, in general, could be controlled by a decrease in the dose of the drug. However, in most cases, this resulted in some loss of clinical effective-

MEDICAL PROGRESS

NEUROLOGY

WILLIAM K. JORDAN, M.D.,* AND H. HOUSTON MERRITT, M.D.†

CLEVELAND AND NEW YORK CITY

DURING the past year significant advances have taken place in many phases of neurology. Increased understanding of the physiology of the cerebral cortex has come from research into the sensory and motor organization of the neopallium of primate brains. New drugs of value in treating myasthenia gravis and states of increased muscular tone have been introduced and more information concerning the use of antibiotics in treatment of infections of the central nervous system has accumulated. These and other studies are discussed under the following headings: biochemistry, physiology and anatomy, pharmacology, infections, cerebrovascular system, convulsive disorders, myasthenia gravis and familial periodic paralysis, multiple sclerosis, and miscellaneous.

BIOCHEMISTRY, PHYSIOLOGY AND ANATOMY

Woolsey and Hines participated in a symposium on the organization of the primate cerebral cortex, which was held under the sponsorship of the American Physiological Society in 1947. In his discussion at the symposium Woolsey¹ summarized new work on patterns of sensory representation in the cerebral cortex. Until recently each of the principal cortical afferent systems was assumed to constitute a main pathway into the cortex and to be singly represented therein. However, in a series of experiments employing the evoked potential technique, Woolsey has shown that touch, vision and hearing, at least, are doubly represented in each hemisphere.

In her comments on motor organization of the cortex, Hines¹ emphasized that in subhuman primates the frontal lobe has acquired almost complete control of movement. In particular, the anterior division of the precentral motor cortex has assumed the activation of the least stereotyped varieties of extrapyramidal action and also, that aspect of control of inhibitory action against tone which is unassociated with the pyramidal system. She also pointed out that the posterior division of the precentral motor cortex has a basic organization characterized by localization of both motor activity and inhibitory action against tone. These localized activities are dependent upon the

integrity of the corticospinal system. In addition to this discrete organization of skeletal muscle control, there exists, in the same cortical field, a mass organization that survives pyramidal section and is capable of producing not only nonlocalized motor action but also nonlocalized inhibitory action against tone. Both these systems play their part in the control of movements. Under no known experimental conditions can the electric stimulation of extrapyramidal motor fields yield localized contraction of skeletal musculature. Indeed, Hines states it is the discrete organization of skeletal muscle that distinguished area 4 or the precentral gyrus from all the remaining motor fields of the neopallium of the primate cerebral cortex.

Recent work by Sugar, Chusid and French² has afforded further proof that double representation of function in the cortex is not limited to sensation. These workers have described a second motor cortex in the monkey (*Macaca mulatta*), lying on the lateral (exposed) and medial (buried) walls of the frontoparietal operculum, and in the posterior portion of the insula. The arrangement of representation of body parts in this area corresponds roughly to that present in the second sensory cortex of the monkey which is posterior to this newly described motor area, and slightly overlaps it. The movements elicited from the second cortical motor area were isolated and contralateral.

Evidence that cortical organization is primarily vertical rather than horizontal has been found by Sperry.³ This investigator crisscrossed the cortex with a knife penetrating through into the white matter, and found that no impairment of motor function or sensorimotor integration is evident after an interval of a month.

Ward McCulloch and Magoun⁴ have announced that a resting tremor, abolished by movement, has been produced in monkeys by destruction of a small area in the midbrain and pontile tegmentum without injury to the corpus striatum, subthalamus or substantia nigra.

Further evidence for localization in the cerebellum has been introduced. Nims and Nulsen⁵ have found that in cats each muscular contraction elicited from the cerebral cortex can be inhibited by stimulation of a topical area of the cerebellum with precise localization.

*Research fellow in psychiatry, Western Reserve Medical School, Cleveland; assistant physician, Division of Psychiatry, Lakeside Hospital, Cleveland.

†Professor of neurology, College of Physicians and Surgeons, Columbia University; director of the Service of Neurology, New York Neurological Institute, Presbyterian Hospital, New York City.

In an important monograph recently published, Lorente de Nó⁶ has detailed the results of a decade of research into the physiology of nerve. It is impossible to summarize the many contributions described in his monograph, which will be consulted by everyone interested in this field of investigation. Among other findings, Lorente de Nó has adduced evidence that the membrane potential of a resting nerve is maintained by some component of its oxidative metabolism, rather than by diffusion potentials or Donnan equilibria resulting from the distribution of cations and anions across the cell membrane.

Hydén⁷ has described the results of cytochemical experiments on nerve cells in which the ultraviolet spectrophotometric technique developed in Caspersson's laboratory were utilized. Nucleotides and certain proteins have convenient absorption ranges for study with these procedures. Hydén has found that, in the course of intense muscular work, there is a sharp decrease in the content of protein and nucleic acids in the cytoplasm of anterior-horn cells. Acoustic stimulation of guinea pigs with tones of various frequencies and intensities produces extensive cytochemical changes in the nerve cells of the cochlear ganglion. After exposure to a tone of a frequency of 6000 cycles per second, and intensity of 80 decibels, for three hours, the ganglion cells pass through a cycle of changes, with decreases in nucleotide and protein concentrations, which reach a maximum in the second week after stimulation. Concentration levels of protein and nucleotide are restored to those of nonstimulated controls within the third week after stimulation. Electroaudiogram studies done on the stimulated animals showed no decrease of auditory functions below those of nonstimulated animals, in the period after stimulation during which cochlear ganglion-cell protein and nucleotide concentrations were decreased.

Hydén⁷ has also found that the neurones of patients suffering from long-standing manic-depressive and schizophrenic psychoses have lower protein and nucleotide contents than those of controls. Treatment of patients with these psychoses by means of malonitrile, considered a precursor of certain nucleotides, is reported to produce varying degrees of beneficial psychic stimulation. It is understood that certain issues involved in these observations on psychotic patients are not yet entirely clarified.

De Robertis and Schmitt⁸ have described the presence of tubular structures in invertebrate and vertebrate nerve preparations studied with the electron microscope. They consider these to be located intraneuronally and to be of possible significance in neural conduction.

A change in the quality of pain sensation is present in a number of clinical conditions in which there has been injury to, or disease of, the central

or peripheral nervous system. In a study of the anatomic basis for alterations in quality of pain sensibility, Weddell and his collaborators⁹ have studied the histologic appearance of areas of skin in the territory of recovering nerve lesions, and of scar tissue from cutaneous scars, in a total of 59 patients, and have correlated their anatomic findings with the results of sensory stimulation. They found that in every case in which an unusually unpleasant quality of pain could be elicited by means of a needle prick, the underlying nerve terminals subserving pain were isolated from their neighbors and no overlapping of terminals was present. Conversely, in no case in which this isolation was not found microscopically, could pain of unpleasant quality be produced. It was also found that alterations in the quality of pain sensibility were not correlated with the presence of morphologically abnormal pain endings. Such endings, however, were associated with disturbances of the threshold of pain sensibility.

This pattern of innervation found in areas of abnormal sensation offers marked contrast with that of normal skin, which has been extensively investigated by Weddell¹⁰. He has found that in normal skin the network of nerve endings subserving the sensation of pain is disposed in such a manner that any one area of skin is supplied by several overlapping terminals derived from different axons.

Thus, these investigators conclude that the occurrence of "over-reaction" to painful stimuli in various clinical conditions is caused by a "reduction in the normal pattern of impulses presented to consciousness," and present the hypothesis that abnormal sensation of pain in association with central disturbances—for example, in the "thalamic syndrome"—is associated with a "reduction in pattern" through damage to particular central nervous pathways.

Feindel et al¹¹ have introduced the use of methylene blue injected into an experimental subject before death as a method of staining nervous tissues *in vivo*.

PHARMACOLOGY

In the course of an investigation into the pharmacology of glycerol ethers, Berger and Bradley¹² made the observation that a beta-dihydroxy-gamma-(2-methylphenoxy)-propane, subsequently named "myanesin," causes a transient relaxation and paralysis of certain skeletal muscles in dosages that do not affect the diaphragm and intercostal muscles, blood pressure or state of consciousness. This drug has been taken up quickly by clinicians, and is reported as useful in producing relaxation during light anesthesia,¹³ in spastic conditions,¹² in diminishing parkinsonian tremor and thalamic pain states¹⁴ and in halting jacksonian seizures.¹⁵

Early reports on myanesin¹⁵ stressed the fact that limitations to usefulness of the drug lie in its inefficacy after oral administration and in its evanescent action intravenously. However, a recent report by Berger and Schwartz¹⁶ maintains that in proper dosages and preparations the drug is effective orally in many patients, and that a more or less constant action can be achieved by repeated administrations. These investigators give myanesin in a 33 per cent (weight in volume) solution in 20 per cent (volume in volume) aqueous propylene glycol, with syrup of cherry 20 per cent (volume in volume) to improve taste of the mixture. The usual dose employed by Berger and Schwartz is 30 cc of this mixture, which contains 1 gm of myanesin. The medication is repeated as necessary, in some cases Berger and Schwartz have given it as many as five times daily. Although myanesin apparently has a low toxicity and wide margin of safety¹² the drug is not without serious side effects. One death has been attributed to the compound¹⁷. Wilson and Gordon¹⁸ report that red-cell fragility is increased, and that there is demonstrable hemolysis in the blood stream of children given myanesin intravenously. On the other hand, Berger and Schwartz¹⁶ state that after oral administration there is no hemolysis. However, they warn of the possibility of as yet undemonstrated toxic effects of myanesin in patients who receive the drug over a long period.

The mode of action of myanesin is not yet clear. Stephen and Chandy¹⁴ have reported that the drug has no action on the transmission of nervous impulses along nerve trunks, across myoneural junctions or on synapses involved in spinal reflexes. Mallinson¹³ has pointed out that it differs in its mode of action from that of curare not only in an absence of effect on myoneural junctions but also in inducing relaxation of abdominal muscles without concomitant intercostal paralysis. Hunter and Waterfall¹⁵ have stated that myanesin when given into an antecubital vein to several patients stopped jacksonian seizures in thirty seconds, an interval slightly in excess of the time they have established as arm-brain circulation time. They consider this to be presumptive evidence for a central action of myanesin, in view of Stephen and Chandy's¹⁴ demonstration of the absence of a more peripheral effect.

Parapanit, a drug employed in Europe in the production of relaxation of skeletal muscle, has been reported as not acting through the myoneural juncture.¹⁹

Telfer²⁰ has stated that the use of BAL in lead poisoning gives encouraging results, and reports of its use in arsenical intoxications have appeared.²¹

Wollenberger²² has reported that the cardiac glycoside ouabain, in low concentrations, increases the oxygen uptake of guinea-pig cortex slices, in

the presence of glucose, pyruvate or lactate. In higher concentrations, an initial increase of respiration of the cortical slices is followed by a depression. However, Wollenberger found that the glycoside has no effect on the respiratory activity of homogenized brain tissue or of isolated oxidative enzymes. He has concluded that ouabain does not directly affect the catalytic function of respiratory enzymes, but that its influence on respiration of brain slices is dependent upon the integrity of cellular structures, the site of action of the drug presumably being at the cell surface. The increase in cell respiration is perhaps due, at least partially, to facilitation of entry of exogenous substrate into the cell, the subsequent depression of respiration resulting from the loss of one or more diffusible respiration catalysts.

In connection with Wollenberger's observations, it is interesting to note that Gold et al²³ have reported that ouabain as well as several other digitalis glycosides, produces convulsions in rats.

CEREBROVASCULAR SYSTEM

A complete report by Kety and Schmidt²⁴ has appeared on the nitrous oxide method for quantitative determination of cerebral blood flow in man. This procedure is based on determination of the rate at which nitrous oxide breathed in a gaseous mixture at low concentration equilibrates with brain tissue. This equilibration occurs within ten minutes, and from a mathematical analysis of the curves of nitrous oxide concentration in arterial and venous blood during this period, and the use of Fick's principle, the cerebral blood flow can be obtained. Kety and Schmidt have checked their method by direct measurement in the monkey with a bubble flow meter, and by a comparison of the brain concentration of nitrous oxide with blood concentration at equilibrium. In 14 healthy young men, cerebral blood flow was 54 cc per minute per 100 gm of brain tissue, with a deviation of plus or minus 12 cc per minute. A mean value of cerebral oxygen consumption was found to be 3.3 cc per 100 gm of brain tissue per minute, with a deviation of plus or minus 0.4 cc. By the use of this procedure, Kety and Schmidt²⁵ studied the effect of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow. Increased arterial carbon dioxide tension produced an increase in cerebral blood flow averaging 75 per cent. High oxygen tensions were associated with a reduction in cerebral blood flow of 13 per cent, whereas anoxemia was associated with an increase of 35 per cent in flow. Measurement of cerebral oxygen consumption showed that no changes occurred in this metabolic activity as a result of changes in arterial tensions of oxygen and carbon dioxide producing the changes in blood flow described.

In a further study, Kety, Shenkin and Schmidt²⁶ studied the relations between cerebral circulation and

intracranial pressure In 12 patients with brain tumors, the rise in cerebrospinal-fluid pressure produced by the brain tumor was associated with a progressive increase in mean arterial blood pressure and cerebrovascular resistance and, above a critical level of cerebrospinal-fluid pressure equivalent to about 450 mm of water, with a definite decrease in cerebral blood flow In this group of patients with increased intracranial pressure, a good correlation between state of consciousness and cerebral oxygen consumption was found The conscious patients yielded a mean value for cerebral oxygen consumption of 3.1 cc per 100 gm of brain tissue per minute, whereas the comatose group averaged 2.5 cc per 100 gm per minute, the average in normals being 3.3 cc per 100 gm per minute Similarly, the patients with cerebral blood flow below 40 cc per 100 gm per minute were all comatose

An interesting study of the physiology of the circle of Willis has been carried out by Rogers.²⁷ Since the time of Willis, who introduced the concept, many have considered that his structure acts as a reservoir, or distributor station, serving equally all vessels leading from it and, consequently, equalizing cerebral blood flow Alternatively, the circle may be conceived as acting merely as an anastomosis, with the potentiality of opening up should a major vessel supplying it be occluded Rogers reports on the anatomy of the structure, injection studies in cadavers, cerebral arteriography in the living and the behavior of a working scale model Anatomically, he has found that the circle of Willis is almost always a closed ring, but that considerable variation occurs in the size of component vessels Injections of methylene blue kept the dye for the most part in the postcircle distribution of the artery, which was injected proximal to the circle In patients on whom cerebral arteriography was done, injections into the carotid arteries on one side was followed by distribution of the injection mass mostly into the middle and anterior cerebral arteries on the side of the injection The working model of the circle of Willis constructed by Rogers gave results in injection experiments similar to those described on cadavers Rogers states that the result of carotid ligation is a reduction of flow in aneurysms of vessels distal to the circle on the side of the ligation, concluding that these findings support the idea that the circle of Willis works as an anastomosis, and not as a reservoir

Although cerebral hemorrhage commonly takes the form of massive intracapsular bleeding in an arteriosclerotic subject in the older age group, less frequently hemorrhage occurs elsewhere in the brain in a young and apparently healthy person Jewesbury²⁸ has discussed the etiology, clinical picture and treatment of the latter group He points out that small intracerebral aneurysms, angiomas and other vascular anomalies have rather fre-

quently been identified as the source of the hemorrhage Less frequently, eclampsia, polyarteritis nodosa, mycotic aneurysm and cerebral tumor are the basis of hemorrhage He states that head injury, even when apparently slight, is an important etiologic factor, and may produce immediate or delayed effects There are a number of cases in which no adequate explanation of the bleeding can be given In the majority of these patients the clinical picture is that of a slowly expanding intracerebral lesion, and not one of sudden apoplexy This kind of clinical picture results from the development of a subcortical hematoma, which tends to become encysted and to increase slowly in size Jewesbury reports a number of cases of this type that have responded well to evacuation of the cyst by surgical intervention

Krainer²⁹ has reported 7 fatal cases of cerebral thrombosis in young Indian adults, 3 of which were due to thrombosis of infected cerebral arteries Two of the patients had syphilis, 1 had cerebral malaria, and 1 had thrombosis in association with a spontaneous aneurysm Three cases were caused by thrombosis of infected cerebral arteries, which were thought to be due to transpulmonary embolism of infective particles, from foci in the systemic circulation

One hundred and thirty patients with subarachnoid hemorrhage have been analyzed by Hamby.³⁰ Forty-four of 47 proved cases were caused by ruptured aneurysms In 23 of 44 fatal cases, intracerebral hematomas were present Of the 130 patients, 67 died in the hospital A follow-up report on 62 of the 63 patients who left the hospital shows that 17 have died Of the 45 living patients, 21 have recovered completely, 13 are able to work despite neurologic handicaps, and 11 are invalids Hamby reports that unfavorable prognostic features are previous attacks, recurrent episodes of bleeding while the patient is in the hospital, and the presence of mental disturbances, unconsciousness and convulsions

Wechsler and Gross³¹ have described the usefulness of cerebral arteriography as both a diagnostic and a therapeutic guide in patients with spontaneous and subarachnoid hemorrhages Subarachnoid hemorrhage was associated with a vascular anomaly in 6 of 10 cases reported, and with an aneurysm in 4

Gilbert and de Takats³² reported on the results of blocking of the cervical sympathetic trunk with procaine on the side of the lesions in 25 patients with apoplexy A transient improvement was noted in 19 patients, manifested by a return of consciousness and of speech, and enhanced motor performance The authors suggest that this procedure, along with other means of combating cerebral edema and stasis, is of value in the treatment of apoplexy

Sindell³³ has stated that 3 patients, in hypoglycemic coma during insulin shock therapy, were brought out of coma by the administration of either amyl nitrite or nicotinic acid, or both. He suggests that the use of vasodilators is valuable in the treatment of patients with apparently irreversible hypoglycemic coma.

The cold-pressor reaction has been studied in psychotic patients with cerebrovascular disease by Becker and his co-workers³⁴. They report evidence that there is an increased response to the vasopressor test in such patients. Persons with well advanced cerebral arteriosclerosis showed the most marked response.

Zeman and Siegel³⁵ have described the development of a permanent paralysis of the right arm in an eighty-three-year-old man with long-standing hypertension following massage, alternately, of the carotid sinuses. They state that 8 cases of irreversible cerebral changes, occurring after carotid-sinus pressure, have been reported in the literature. These accidents have taken place, usually, in elderly patients.

A study of hypertensive encephalopathy has been made by Pickering³⁶. He divided this condition into two distinct forms. In the first form, acute hypertension, or chronic hypertension with an acute exacerbation of hypertension, may be associated with headaches, vomiting, convulsions and coma, as the result of acute edema of the brain. Pickering explains these symptoms on the basis of "defective constriction" of cerebral vessels with the increased intravascular pressure, which is present in association with the hypertension, leading to an outflow of fluid into the brain. In the second form, which is associated with chronic hypertension, Pickering thinks attacks of local motor or sensory paralysis are the result of sudden arterial occlusion of larger or smaller vessels, caused, perhaps, by a thrombus. He attributes the phenomena of hypertensive encephalopathy to mechanisms other than arterial spasm for several reasons. He points out that cerebral vessels have poor musculature, and that they constrict feebly in response to known vasoconstrictor agents. Also in many of his patients with chronic hypertension, Pickering was unable to draw a sharp dividing line between bouts of paralysis lasting for a short while, and those lasting permanently, which he regards as an argument against vasospasm as the cause of the symptomatology.

MYASTHENIA GRAVIS AND FAMILIAL PERIODIC PARALYSIS

Approximately 200 patients with myasthenia gravis have undergone thymectomy as treatment for their disease. Harvey³⁷ has pointed out that 15 per cent of these patients show marked improvement, and has commented that an analysis of why the operation failed to result in marked improve-

ment in the other 85 per cent should be of value in understanding the disease. In discussing the results of thymectomies done at Johns Hopkins Hospital, he states that the two factors most favorable for good response to the procedure are performance of the operation early in the course of the disease and prior administration of only small amounts of neostigmine. Harvey states that it is not necessary for a thymoma to be present for a remission to occur after thymectomy, since some patients whose thymus glands show only moderate hyperplasia also improve. Incidentally, a thymoma, if present, may not be demonstrable by x-ray examination. Histologically, the tumors removed at Johns Hopkins Hospital have shown varying amounts of neoplastic tissue, which arises from epithelial cells of the thymus reticulum, lymphocytic hyperplasia is also present. Patients who have shown a response to thymectomy manifested improvement of strength predominantly in their limb and trunk muscles, with less increase of power in muscles supplied by cranial nerves.

Tetra-ethylpyrophosphate (TEPP), a drug with a powerful anticholinesterase activity, has been introduced recently by Burgen and his colleagues³⁸ for the treatment of myasthenia gravis, and promises to be of considerable value. This drug, whose actions are reported to resemble those of eserine and neostigmine more closely than those of diisopropyl fluorophosphate (DFP), is as potent as eserine and a third as potent as neostigmine in tests on rats. The duration of its action, however, is twenty-four to forty-eight hours, in contrast with the two to three hours that is the period of action of eserine and neostigmine. TEPP is well absorbed when given by mouth.

When given orally to 3 patients with myasthenia, TEPP was found to be a completely effective substitute for neostigmine, and, because of its longer action, its effect was much smoother than that of neostigmine. Burgen et al³⁸ state that they have found 10 mg of TEPP given by mouth to be as effective as oral doses of 100 to 150 mg of neostigmine. The maintenance dose of TEPP varies from 8 to 12 mg daily, administered orally in two or three doses.

The side actions of TEPP consist in visceral and central effects similar to those of neostigmine. The most pronounced side action is on the gastrointestinal tract, colic and diarrhea being produced. This visceral action is prevented effectively by atropine. The central side effects, produced in all of Burgen's patients during dose stabilization, included vertigo and nystagmus. Nausea and vomiting, sweating and pallor also occur. The last two groups of effects were not prevented by atropine.

Grob and his associates³⁹⁻⁴¹ have summarized their extensive clinical research with diisopropyl fluorophosphate (DFP). They find that whereas administration of DFP to patients with myasthenia

intracranial pressure In 12 patients with brain tumors, the rise in cerebrospinal-fluid pressure produced by the brain tumor was associated with a progressive increase in mean arterial blood pressure and cerebrovascular resistance and, above a critical level of cerebrospinal-fluid pressure equivalent to about 450 mm of water, with a definite decrease in cerebral blood flow In this group of patients with increased intracranial pressure, a good correlation between state of consciousness and cerebral oxygen consumption was found The conscious patients yielded a mean value for cerebral oxygen consumption of 3.1 cc per 100 gm of brain tissue per minute, whereas the comatose group averaged 2.5 cc per 100 gm per minute, the average in normals being 3.3 cc per 100 gm per minute Similarly, the patients with cerebral blood flow below 40 cc per 100 gm per minute were all comatose

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phate effects an irreversible inhibition of cholinesterase, the enzyme that hydrolyzes acetylcholine, and thus produces an accumulation of acetylcholine. These workers have correlated their findings with the recent evidence indicating that certain kinds of convulsions are related to abnormalities of acetylcholine metabolism. It is interesting to compare this study with that of Pope et al,⁵⁰ who have shown that in trigger areas of the cortex of animals with experimentally induced focal epilepsy, there is an increase in cholinesterase concentration.

The results of a decade of systematic investigation into the anticonvulsant action of many classes of compounds have been summarized by Merritt and Brenner.⁵¹ Over 700 compounds were first investigated for their action in protection of cats against electrically induced convulsions. About 10 per cent of the 700 compounds were found to produce a significant elevation of the convulsive threshold in acute experiments.

Classes of compounds found to possess activity in raising electrical threshold include barbiturates, benzoxazoles, hydantoinates, ketones, oxazolidinediones and phenyl compounds containing sulfur. So far only a few of these compounds have been tested clinically. Of those tested, 5,5 diphenylhydantoin (dilantin) has proved to be the most effective anticonvulsant yet discovered. Of possible equal or greater value is 5 methyl, 5 phenyl hydantoin. The latter compound is not suitable for general use because of its toxicity.

Ellermann⁵² has reported on the use of 5,5-diphenyl-2,4-dioxazolidinedione (epidone) in epilepsy. Apparently, on the basis of records of patients presented, the drug when administered in dosages of 2 or 3 gm daily is effective in controlling grand-mal and psychomotor seizures. It is not possible from the cases quoted in Ellermann's article to compare the effectiveness of epidone with that of other anticonvulsants such as dilantin, since the patients described were not receiving adequate dilantin therapy at the time they were started on epidone. Ellermann states that toxic reactions with epidone were a fifth as frequent as those with dilantin.

As an assay of the efficacy of anticonvulsants, the activity of various drugs in preventing the tonic phase of electroshock in nonepileptic subjects has been introduced by Toman et al.⁵³

Another fatal case of acute pancytopenia following tridione therapy has been reported.⁵⁴ This brings the total of reported deaths to 3. In a careful and convincing study, Barnett, Simons and Wells⁵⁵ have described a patient who on three occasions developed a nephrotic syndrome following administration of tridione. These reports emphasize the necessity of repeated blood and urine examination in patients receiving this substance.

Russell⁵⁶ has employed a technic of correlating the areas of cortex involved in head wounds with the incidence of post-traumatic epilepsy in patients who have received head wounds. Although casual inspection of the cortical maps presented impresses one with a predominance of involvement in the "suppressor" areas of cortex in patients who develop traumatic epilepsy, R. A. Fisher has analyzed the maps and has concluded that there is no statistically significant difference in location of wounds in the two groups of patients.

Recent work by Elvehjem and his colleagues⁵⁷ at Wisconsin, on the production of running fits in dogs by white flour bleached by the "agene" process with nitrogen trichloride, has aroused interest in the possible role of flour so manufactured in epilepsy in human beings. However, that there is a species difference in the effect of the "agenized flour" is illustrated by the fact that although feeding of this substance to cats and dogs produced fits, monkeys so treated did not develop them but did show some changes in their electroencephalograms, and that 12 human beings fed highly agenized products for two to four weeks did not show either convulsions or electroencephalographic changes.⁵⁷ The fraction of flour showing the toxic factor has been demonstrated to be the wheat protein, and not the lipid or carbohydrate fraction. Of course, epilepsy in its form known today in human patients plagued man long before "agenized" flour was ever manufactured.

Abbott and Schwab,⁵⁸ in analyzing patients with epilepsy showing normal electroencephalograms between seizures, point out that such patients have a better prognosis with respect to frequency of future spell, response to medicine, likelihood of remissions while off medication and capacity for work, than those with abnormal records between convulsions. Their patients with abnormal inter-seizure patterns usually had had convulsions in childhood, or had suffered brain injuries.

INFECTIONS

Reports on the efficacy of penicillin in the treatment of neurosyphilis continue to appear.⁵⁹⁻⁶⁴ Thus, Dattner and his co-workers⁵⁹ report satisfactory results in 151 patients with both asymptomatic and symptomatic neurosyphilis. They employ 40,000 units of penicillin given intramuscularly every three hours for 150 doses, a total of 6,000,000 units, 90 per cent of their patients gave satisfactory responses and these investigators believe that penicillin is as effective as and will eventually replace fever therapy.

Heiman,⁶⁰ however, recommends penicillin for asymptomatic and early symptomatic syphilis, but believes that fever therapy should be used in treating late symptomatic neurosyphilis.

Isolated cases of the apparent cure of tuberculous meningitis have been reported. Mehas and Truax⁶⁵

gravis results in considerable gain in strength, in no case was the improvement as great as that obtained with neostigmine, and they believe that the unpleasant central nervous and gastrointestinal symptoms produced by DFP preclude its use in amounts sufficient to produce therapeutic effects. They have found evidence that DFP and neostigmine compete for cholinesterase (Ch-E) and that formation of a neostigmine-Ch-E complex prevents irreversible inhibition of Ch-E by subsequently injected DFP, thereby blocking the effect of DFP.

Torda and Wolff⁴² have reported that injections of a mixture of essential amino acids effect an increase in strength of patients with myasthenia, presumably through influencing acetylcholine synthesis.

In familial periodic paralysis, the close association of a fall in concentration of serum potassium with the onset of muscular paralysis and the relief of muscle weakness that ensues after administration of potassium salts are both well known and indicate that a defect in potassium metabolism is involved in the pathological physiology of this disease. The nature of the disorder of potassium metabolism is not understood, however.

Danowski et al.⁴³ have studied, in a quantitative manner, the exchange of potassium and sodium between the extracellular and intracellular phases of the body fluids in 2 patients with this disease. They found that during the development of paralysis, potassium shifted from the extracellular to the intracellular phase, with a resultant sharp decline in serum potassium concentrations. During recovery, large amounts of administered potassium were taken up by the intracellular phase before extracellular loss was replenished. Reciprocal transfer of sodium was observed in one patient, but not in the other. No significant changes occurred in the volume of total body water and extracellular fluid, and there was no increase in potassium excretion in urine or feces.

Gass et al.,⁴⁴ in a study of a patient with familial periodic paralysis by means of radioactive potassium, were unable to detect, with a surface Geiger counter, any increase in radioactivity over either muscles or liver in an induced attack of paralysis. Nor could they find a shift of potassium into spinal fluid or red cells. Thus, although from the study of Danowski and his co-workers⁴³ it appears clear that during an attack of paralysis potassium moves into the intracellular phase of the body fluid of the patient, and is not excreted in the urine or feces, on the basis of Gass's work it is not possible to determine into which particular organ or cellular system the potassium migrates. It should be pointed out that there are certain equivocal aspects to the observations of the latter investigators, and further studies with tracer or other appropriate technics may well show that the potassium moves into the muscle at the onset of paralysis.

MULTIPLE SCLEROSIS

Although previous reports have described the production of such lesions in monkeys by similar methods, the production of disseminated encephalomyelitis in rabbits by the injection of homologous spinal-cord homogenates with adjuvants has now been reported by Morrison.⁴⁵

Langworthy⁴⁶ has discussed a number of patients suffering from multiple sclerosis who showed signs of conversion hysteria either before or after the development of signs of organic disease. These patients also manifested pronounced evidences of vasomotor instability in their extremities, and Langworthy asks whether vascular changes in the brain related to neurotic difficulties may not lead in turn to organic disease. Langworthy believes that psychotherapy offers as hopeful an approach to the therapy of multiple sclerosis as any other treatment now available.

Eighteen patients with multiple sclerosis who showed constrictions of retinal arterioles have been reported by Franklin and Brickner.⁴⁷ In one of their patients, constriction was seen in a retinal venule. Frequently, scotomas and, occasionally, a reduction in visual acuity, associated with the arteriolar constriction, were also present. The objective findings are stated to have coincided with the subjective complaints of the patients. In most cases in which they were employed, fast acting, vasodilating drugs such as amyl nitrite, administered by inhalation, caused prompt, temporary relaxation of the arteriolar constrictions and, concomitantly, a reduction in the size of the scotoma. In several cases, an increase of visual acuity was noted in patients in whom a reduction of acuity was associated with arteriolar constriction. Franklin and Brickner regard the constrictions as spasms of arterioles, and they develop the hypothesis that the lesions throughout the central nervous system in multiple sclerosis are caused by diminution of the blood supply to neural tissue resulting from vasospasm.

In an investigation of the loss of axis cylinders in sclerotic plaques by means of the Bodian silver stain, Putnam and Alexander⁴⁸ state that some degree of damage or destruction of axons occurred in all the sclerotic plaques investigated. Similar changes of a corresponding degree of intensity were seen in other central-nervous-system lesions of vascular origin.

EPILEPSY

Himwich and his colleagues⁴⁹ have described the appearance of high-amplitude waves of grand-mal type in the electroencephalogram of rabbits after the injection of di-isopropyl fluorophosphate into a carotid artery. The high-amplitude waves appear first in the cortex on the injected side, subsequently spread to the opposite cortex and are maintained for an hour. Di-isopropyl fluorophos-

The clinical characteristics of an epidemic of Japanese B encephalitis occurring as an outbreak in the civilian population of Okinawa have been reported by Lewis et al.⁷⁵ Among 63 patients, most of whom were children, the mortality was approximately 20 per cent. The clinical manifestations were characteristic of a diffuse encephalomyelitis and resembled those of other neurotropic virus infections. Permanent disorders of the nervous system of variable degree resulted in a fifth of the patients. A postencephalitic parkinsonian syndrome occurred rarely. It was found that accurate diagnosis depended upon the use of specific serologic and virologic tests.

Gibbs and Gibbs⁷⁶ have analyzed the electroencephalographic findings in 240 cases of encephalitis in various stages of the disease. They state that the abnormalities are often focal and can be correlated with the stage of the disease. During the acute and subacute phases the electroencephalographic findings correlate with the general severity of symptoms. However, the only feature of the postencephalitic syndrome that correlates highly with electroencephalographic abnormality is the presence of convulsions. The electroencephalogram has diagnostic value for encephalitis, and after the acute phase is past it has prognostic value for postencephalitic epilepsy. Wave and spike activity of the petit-mal type is a common sequel of encephalitis in children.

Hoyne and Schultz⁷⁷ have reported the case of a patient who had five attacks of meningitis in five years, four of them resulting from a pneumococcus, and the fifth from *H influenzae*. At autopsy, two small, inexplorable perforations were found behind the crista galli that led into the ethmoid cells and nasopharynx. The authors suggest that every patient with pneumococcal meningitis have skull x-ray films taken with special reference to the sinuses.

MISCELLANEOUS CONSIDERATIONS

Neuropathological aspects of thrombocytic angiiothrombosis have been detailed by Adams, Cammermeyer and Fitzgerald.⁷⁸ This name is applied to a rare disease, of which 13 cases are described in the literature. The etiology is unknown. The disease is characterized by fever, malaise and cerebral symptoms ranging from muscular weakness, hemiplegia, convulsions and confusion to coma. Hematologically, an anemia and thrombopenia are present. The disease runs a rapidly progressive course, death ensuing in from a few days to eight weeks. Neuropathologically, platelet thrombi are found in cerebral vessels, sometimes associated with multiple small foci of parenchymal necrosis and petechial hemorrhages. A clinicoanatomic correlation of neurologic symptoms is usually not possible. This condition must be distinguished clinically from idiopathic thrombopenic purpura,

lupus erythematosus subacute bacterial endocarditis and rickettsial infections. The differentiation may be possible on the basis of the total clinical picture and laboratory data. The diagnosis could probably also be established by bone-marrow autopsy, since platelet thrombi and vascular hyperplasia are often observable in the bone marrow.

Bethell and Sturgis⁷⁹ have described 70 cases of pernicious anemia studied over periods of not less than ten years. Most of the patients, whether treated with oral preparations of stomach or liver, or parenteral crude or refined liver extracts, showed significant improvement in their neurologic manifestations. The period of improvement was limited essentially to the first year of therapy. Thirty-six patients who had regular therapy and complete hematologic remission afforded no case of development or progression of neurologic symptoms, 15 patients who did not adhere to optimal therapy, and who had abnormal blood values, showed transient and reversible neurologic manifestations, which cleared up on resumption of therapy, and 19 patients who suffered clinical and hematologic relapses manifested only rarely serious progression of neurologic disease. However, the authors point out that these results do not justify the conclusion that irregular or suboptimal therapy of pernicious anemia is without serious possibilities.

Ross and his collaborators,⁸⁰ reporting on the use of folic acid in the treatment of pernicious anemia, state that 11 of their patients developed, or showed progression of, subacute combined degeneration of the spinal cord during folic acid therapy. Neurologic involvement developed in most of these patients when the peripheral blood was normal. The institution of liver-extract therapy, in addition to folic acid maintenance therapy, failed to prevent progression of the disease in 4 patients, and only partially arrested the disease in the fifth, in whom, indeed, improvement occurred more rapidly when folic acid was discontinued. In the experience of these physicians, subacute combined degeneration of the spinal cord occurred with greater frequency in patients on large daily doses of folic acid than it did in patients with small or intermittent doses. They suggest that folic acid in large daily doses may actually precipitate or aggravate neurologic disease.

Friedman and Brenner⁸¹ report that the intravenous injection of 100 mg of sodium nicotinate did not produce relief of pain in any of 7 patients suffering from acute migraine attacks. These investigators did not find this compound to be any more effective in the symptomatic relief of patients with psychogenic or post-traumatic headache than physiologic solution of sodium chloride injected intravenously in small amounts.

Mills⁸² has reported that potassium thiocyanate is of some value in the relief of headaches suffered by patients with benign and malignant hyperten-

have described a thirty-one-year-old woman with proved tuberculous meningitis in whom intramuscular and intrathecal streptomycin apparently arrested the progress of the disease. Appelbaum and Halkin⁶⁶ report the case of a nine-year-old boy with tuberculous meningitis and pulmonary miliary tuberculosis whose disease was completely arrested by intrathecal and intramuscular administration of streptomycin. Although in the former patient residual damage to the central nervous system was present, in the latter there were no neurologic residua.

Now that there is a hopeful therapeutic procedure for this previously incurable malady, the necessity of early diagnosis of tuberculous meningitis increases. This is especially true since the chance of avoiding serious, permanent, neurologic sequelae probably depends on early institution of therapy.⁶⁷ Tuberculous meningitis is commonest in the first decade of life, and therefore it is in young children that particular watch must be kept for early signs. It has been emphasized⁶⁷ that the presenting features of tuberculosis of the meninges are many and varied, but that most cases conform to a general pattern of symptomatology. Most often the meningitis begins insidiously, with symptoms mimicking minor ailments. Rarely, the onset of tuberculous meningitis is sudden, with focal signs in the nervous system, such as cranial-nerve palsies, limb paralyzes and focal and generalized convulsions. Headache, fever and stiff neck are frequently present. Demonstration of a low and falling spinal-fluid sugar value is of great diagnostic help in early stages.

Paine et al⁶⁸ have described the use of streptomycin in the treatment of certain gram-negative bacillus infections of the central nervous system. Two patients with *Pseudomonas aeruginosa* infection, 2 with Type B *Haemophilus influenzae* infections, and 1 patient with *Proteus vulgaris* infection all recovered after treatment with streptomycin. Streptomycin was given intrathecally in doses of 0.05 gm in 1 cc of sterile physiologic saline solutions daily. Concomitantly, streptomycin was administered intramuscularly in doses varying from 0.02 gm to 4 gm every six hours. The fact that fever may rise during streptomycin therapy, as a result of drug toxicity, makes it difficult to decide at what point treatment should be terminated. Frequent cultures of the spinal fluid are a helpful guide in making this decision.

Hoyne and Brown⁶⁹ have reported a series of 30 patients with type B *H influenzae* meningitis, 28 of whom recovered after treatment with various combinations of specific serum, sulfonamides and streptomycin. They emphasize particularly that 23 of the 28 patients who recovered received no intrathecal therapy.

Accounts of the involvement of the nervous system in trichiniasis have recently appeared

MacAndrew and Davis⁷⁰ have reported the case of a thirty-nine-year-old woman with trichiniasis whose presenting symptoms were right footdrop and right-facial-muscle palsy. These writers point out the importance of consideration of this disease in diagnosis of patients with unexplained neuritis. Skinner⁷¹ has described 2 cases of depression and delirium in which trichiniasis was present. The clinical condition of 1 of the patients resembled delirium tremens.

Collard and Kendall⁷² have presented the case of a patient with cerebral amebiasis whom they successfully treated with emetine. The authors state that this patient is the first reported in the literature who has recovered from amebiasis of the central nervous system. This condition has had a fatal outcome even after therapy with emetine or evacuation of amebic cerebral abscesses neurosurgically in all patients heretofore reported. Collard and Kendall attribute the recovery of their patient to early institution of treatment, probably at a stage of focal amebic encephalitis, before actual abscess formation had occurred.

A comprehensive report on involvement of the nervous system in schistosomiasis has been made by Kane and Most,⁷³ who point out that the three species of schistosome demonstrate predilections for localizing in different parts of the central nervous system. Thus, *S japonica* invades the brain, whereas *S mansoni* and *S haematobium* go invariably to the spinal cord. Correspondingly, the symptomatology varies, *S japonica* manifesting itself by diffuse encephalitic symptoms, focal paralyzes, epileptic seizures or signs of an expanding intracranial lesion. On the other hand, *S mansoni* and *S haematobium* produce signs of myelitis or spinal-cord compression. The authors emphasize the fact that the diagnosis of this condition should be considered in any patient with these findings who has been exposed to possibly infected fresh water in any one of the endemic areas in the South Pacific Area (Japan, Formosa, China and the Philippines). It may be as long as four years after infection before central-nervous-system involvement is manifested. The treatment described by Kane and Most consisted usually in administration of antimony potassium tartrate, accompanied, if the clinical condition made it necessary, by appropriate surgical intervention. Prognosis is usually good for arrest of the disease but, of course, neural tissue destroyed before treatment is instituted will not be restored.

A patient with a large granulomatous tumor in the right occipitoparietal region of the brain, caused by infestation with *S japonica*, has been described by Reeves and Kerr.⁷⁴ The preoperative diagnosis was an expanding intracranial lesion, and the possibility of its being on the basis of schistosomiasis was not seriously considered, since no historical or clinical evidence pointed to the parasite, except for exposure in the endemic areas of Leyte and Mindoro.

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sion Symptomatic relief resulted in patients in whom no fall of blood pressure was noted Administration of thiocyanate afforded no relief of headache in patients with malignant hypertension whose blood urea nitrogen was elevated

Dow and Whitty⁸³ have made an electroencephalographic study of 51 patients with migraine headaches Generalized dysrhythmia was observed in 14, symmetrical, bilateral, episodic, abnormal activity in 12, and a persistent abnormality in 4 Exaggeration of a previous abnormality was noted at the period of aura in 5 of 8 cases, and after ergotamine tartrate administration in 3 of 5 cases The transient focal abnormality described by Engel et al⁸⁴ was not observed

A simple classification of headaches has been suggested by Butler and Thomas⁸⁵ on the basis of mechanism of their production These authors suggest dividing headaches into vascular headaches, including migraine, histamine, cephalalgia and tension headache, psychic headache, intracranial traction headache, extracranial headache due to irritation of afferent cranial or cervical nerves, combined intracranial and extracranial headache, and toxic or mixed headache

Robertson et al⁸⁶ have investigated the nature of pains in the head and face arising from diseased or experimentally stimulated teeth Head pain associated with prolonged toothache and located at a distance from the painful tooth itself was found to be of two types The first is that associated with sustained contraction of muscles of the head and neck, and the second that which is on the basis of referred pain in the distribution of the trigeminal nerve

Ingraham and Cobb⁸⁷ have reported on their clinical experience with diodrast in cerebral arteriography, and state that this substance is safer than thorotrast and is as satisfactory in this procedure

Falconer, McGeorge and Begg⁸⁸ have published a description of their extensive and careful study on the problem of ruptured intervertebral disk in the lumbar region of the spine The results of routine myelography, done on patients suffering from low back pain, or sciatica, and admitted to the hospital because of severity or intractability of their symptoms, indicate that almost all such patients have intraspinal lumbar disk protrusion A protruded disk may cause only low back pain, presumably through implication of the sinu-vertebral nerve However, sciatica itself is produced only when the disk prolapse is so situated that it impinges upon a nerve root in its extrathecal course at the level of either of the lower lumbar vertebral disks Secondary changes, probably on the basis of intraneural edema, appear within the affected nerve root, contributing to production of symptoms by pulling the nerve root tightly against the prolapsed disk and thus causing an angulating strain In this manner pain fibers may be excited, and a

block in neural conduction may be produced, thus accounting for certain of the sensory, motor and reflex disturbances seen in this condition Resolution of these intraneural changes may result in spontaneous remission of clinical symptoms It is interesting to note that in Falconer's series spontaneous remission of symptoms occurred in patients at a time when a prolapsed disk was still demonstrable by myelography

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 35061

PRESENTATION OF CASE

A seventy-one-year-old unmarried woman entered the Tumor Clinic complaining of episodes of bloating and vomiting.

During the three months before admission to the Tumor Clinic she had experienced bouts of bloating, with nausea and vomiting, precipitated by food or drink. These episodes lasted only about one day and recurred on the average of once every three weeks. At the onset of the difficulty she had also noticed a feeling of pressure on the bladder, associated with urinary incontinence. About thirty years before admission she noticed moderate painless hematuria. About ten years later a suprapubic operation was done, and a "small growth" was removed. Her physician informed her that there would be a tendency for the tumor to recur, and she returned for many transurethral treatments for the purpose of cutting down the tumor. About sixteen years before admission she was told that the right ureter was closed. Operation was performed, and the ureter opened. It was kept dilated by cystoscopies and passages of ureteral sounds at weekly intervals and later less frequently. About three years before entry to this hospital, following an episode of hematuria, she entered another hospital, where two papillomatous tumors were removed from the bladder by suprapubic operation. At that time no function of the right kidney was demonstrable by intravenous pyelogram. About ten months later she re-entered the same hospital, complaining of a "lump" in the right side. A right nephrectomy and ureterectomy were done. The pathological report was "papillary carcinoma of pelvis and kidney."

Examination in the Tumor Clinic revealed an incisional hernia of the lower mid-abdomen and a firm, movable mass, about the size of a grapefruit, which could be ballotted between the abdominal and pelvic examining fingers on vaginal examination. On barium enema there was a large, extrinsic, tumor mass that displaced the rectum and lower sigmoid to the left. On intravenous pye-

lography the left kidney showed a slight dilatation of the calyces and pelvis, the right kidney was not visualized. The mass in the pelvis had displaced the left ureter laterally, and there was questionable slight compression of the lower third of the left ureter. It also depressed the roof of the bladder. There was generalized osteoporosis of the bones of the lumbar spine and pelvis but no definite evidence of metastases. A chest film showed clear lungs. The heart was slightly prominent in the region of the left ventricle. A gastrointestinal series was negative except for a moderately large, easily reducible hiatus hernia. She was followed in the Tumor Clinic for about two months and then admitted to the hospital.

Physical examination revealed a thin woman. Abdominal examination disclosed a large, "cystic-feeling," movable, multilobular mass, apparently arising from the pelvis. On pelvic examination a mass was felt in the cul-de-sac, apparently connected with the abdominal mass.

The temperature was 99.8°F, the pulse 96, and the respirations 22. The blood pressure was 208 systolic, 90 diastolic.

Examination of the blood showed 12.2 gm. of hemoglobin and a white-cell count of 7500. The urine specific gravity was 1.004. The sediment contained 30 to 40 white cells per high-power field. The serum nonprotein nitrogen was 31 mg., and the total protein 6.3 gm. per 100 cc. The chloride was 106 milliequiv. per liter, and the prothrombin time was 22 seconds (normal, 16 seconds). A phenolsulfonphthalein test showed 40 per cent excretion of the dye in ninety minutes. An intravenous pyelogram, repeated about two and a half months after the one done in the Tumor Clinic, showed poor concentration of the dye. There was marked dilatation of the calyces and pelvis. Only the upper third of the left ureter was seen, and this was dilated. The bladder was depressed but showed no definite defects. The mass in the pelvis had tripled in size since the time of the previous examination. A cystoscopy showed that only a third of the bladder mucosa could be visualized, no abnormalities were noted. The left ureteral orifice appeared normal. The mass in the pelvis so compressed the bladder that complete examination was not possible.

On the fifth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. WYLAND F. LEADBETTER. We have several things to explain in this case: the episodes of vomiting, the mass in the pelvis, and the developing hydronephrosis and hydroureter on the left side. So far as the first part of the history is concerned, it seems quite obvious that for thirty years the patient suffered from recurrent tumors of the bladder. The type of tumor that might give rise

to recurrences without serious manifestations is a papillary tumor. It may have begun as a true papilloma of low-grade malignancy, or may have recurred as a papilloma or later as a papillary carcinoma. In any case, for fifteen of the thirty years she received treatment for recurrent bladder tumors.

Sixteen years before the last admission it was found that obstruction existed in the lower right ureter incident to either growth of the tumor or treatment thereof. I assume that as a result of the removal by fulguration or electroresection of one of the tumors the right ureteral orifice became scarred and ultimately closed. Operation was carried out to correct this obstruction, and the result must have been fairly satisfactory because up to three years before this admission cystoscopy was done at gradually increasing intervals for dilatation of the ureter. Hematuria recurred at this time, and the patient was found again to have a papillary tumor of the bladder. This one was removed by suprapubic operation. At that time no function was demonstrated in the right kidney. This brings up the point that many papillary tumors of the urinary tract may have their origin in the renal pelvis or ureter with secondary involvement of the bladder. Whether bladder tumors under these circumstances arise independently as a result of some carcinogen excreted in the urine or by implantation of tumor cells on the bladder mucosa from the renal pelvis or ureter, I do not know. In any case, we have found from experience that if we are dealing with a papillary tumor of the bladder we must at least obtain an intravenous urogram to determine whether there is evidence of tumor in the upper urinary tract. In a significant number of cases we find associated papillary tumor of the renal pelvis or ureter. In the case under discussion there was a papillary tumor of the right renal pelvis or ureter, because two years before the patient entered this hospital a nephroureterectomy was done. The record states that a "papillary carcinoma of the pelvis and kidney" was found. It would be interesting to know whether the ureter was involved because it might have a bearing on subsequent events. If transection of the ureter occurred through tumor, or if tumor cells from the ureter were spilled, it is possible that a recurrence of papillary carcinoma took place outside the bladder wall in the pelvic tissues. Up to this point in the case we can be quite certain of the state of affairs.

When the patient came to the Tumor Clinic it was found that she had a firm, movable mass about the size of a grapefruit in the pelvis. This could be palpated easily on combined abdominal and vaginal examination. It implies that the tumor was not deeply infiltrating or fixed to the pelvic wall. There is no statement referable to the pelvic organs, which is unfortunate because there is no way of knowing whether there was disease of the uterus or adnexa.

It therefore seems impossible to make a definite diagnosis.

DR TRACY B MALLORY: Can you give us any further information on that point, Dr Sturgis?

DR SOMERS H STURGIS: No. I just saw her on entry to the hospital two months later.

DR LEADBETTER: I think one can assume that this mass did not suggest disease of the cervix. I do not think we can carry it any farther than that. A barium enema showed nothing in the lower bowel. Intravenous pyelograms showed dilatation of the left renal pelvis and ureter. There could have been intrinsic disease of the left lower ureter or pressure on the ureter by the mass in the pelvis. A mass of this size would cause pressure on and distortion of the bladder.

There was generalized osteoporosis of the bones of the lumbar spine and pelvis, but no definite evidence of metastasis. I do not like the statement "no definite evidence." It implies to one reading the record that the radiologist was suspicious of metastatic disease in the bone but unwilling to commit himself. The chest films were normal. A gastrointestinal series was negative except for hiatus hernia, which probably has no bearing on our problem. In the two months that intervened between examination in the Tumor Clinic and entry to the hospital, the pelvic mass changed markedly in size, consistence and configuration. What happened during the two-month interval is difficult to say. If we are dealing with cancer, necrosis or hemorrhage or both may have occurred, or the tumor itself may have simply grown tremendously.

The presence of white cells in the urine is not significant since it is improbable that cystoscopic treatment could have been repeatedly carried out for thirty years without some infection being present. One is obliged to make the diagnosis of cystitis, and possibly, of low-grade pyelonephritis of the left kidney. The nonprotein-nitrogen was normal but the phenolsulfonephthalein test showed diminished excretion in ninety minutes. An intravenous urogram showed poor function, with dilatation of the pelvis and ureter, which had increased a great deal in two months. Cystoscopy was reported to allow incomplete visualization of the bladder interior, but no abnormalities were noted.

The question of tumor involving the bladder wall comes up, and with the information at hand it is difficult to be sure that such a tumor was not present. It is a possibility. In view of the dilatation of the left upper urinary tract, it would be desirable to know whether intrinsic disease of the left lower ureter existed. It could have been determined by ureterogram. I would not have wanted to operate without knowing something more about this.

From the standpoint of diagnosis my explanation seems too easy to be true and there is probably some catch, but I think the most likely possibility is that

recurrent papillary carcinoma developed outside the bladder wall in the tissues behind the bladder, either from spillage of cells at the time of ureterectomy or from tumor cells in the intramural ureter, which may not have been removed. If we knew the condition of the pelvic organs prior to the development of the mass, diagnosis would be much easier.

For the sake of completeness we have to consider other possibilities. Since papillary tumors of the bladder had been repeatedly treated, it is possible that extension through the bladder wall occurred, even though the bladder lumen showed no evidence of tumor. Involvement of lymphatics in the pelvis is possible. The mass may have originated in the iliac or hypogastric glands, but the description of the mass as ballotable leads one to believe that it did not arise in the pelvic wall itself. It could have been, I suppose, an ovarian neoplasm or a mass in the fundus of the uterus. We have to consider the sigmoid as the point of origin in spite of the normal barium enema — cancer of the bowel or an abscess arising in an infected diverticulum of the sigmoid. These possibilities seem very unlikely. A diverticulum of the bladder, with a very tiny communication with the bladder, and a perivesical abscess originating in infection at the time of operation two years before, are remote possibilities. Lymphosarcoma, retrovesical sarcoma or sarcoma arising in the bladder wall are mentioned but excluded because of the lack of fixation of the mass. A ruptured aneurysm of a pelvic vessel is dismissed as extremely unlikely.

DR F DENNETTE ADAMS: Would you expect carcinoma — that is, recurrent carcinoma — to be as movable as this mass was?

DR LEADBETTER: Papillary carcinoma may not be a markedly infiltrating tumor. It may form a mass without extreme fixation.

DR LANGDON PARSONS: How often do tumors of the genitourinary tract metastasize to the ovary?

DR LEADBETTER: I have never seen it, but in going over a series of 100 cases of bladder cancer autopsied at the Johns Hopkins Hospital, I believe I found 2 or 3 cases metastasizing to the ovary.

DR JOE V MEIGS: A Krukenberg tumor of the ovary may come from a tumor of the stomach, uterus, bile ducts or rectum, but I never remember it from the kidney or ureter. I think it could happen.

DR LEADBETTER: I should have mentioned the possibility of carcinoma of the gastrointestinal tract with peritoneal implant in the cul-de-sac.

DR MEIGS: There was no blood in the urine to any extent, which might be odd if the tumor extended directly from the bladder to the pelvic wall.

DR LEADBETTER: Yes.

May we see the x-ray films?

DR STANLEY M WYMAN: The lung fields are clear. The heart is definitely enlarged, but with-

out characteristic configuration. The barium enema outlines an ill defined, soft-tissue mass occupying most of the pelvis centrally, displacing the sigmoid and rectum toward the left, but it does not appear to involve the colon intrinsically. The first pyelogram shows prompt excretion of dye by the left kidney, with blunting of the minor calyces, slight widening of the major calyces and definite displacement of the left midureter. The left ureter can be seen on a later film, displaced far to the left. In the left pelvis the bladder shadow shows some compression laterally. Again the outlines of the mass in the pelvis are indistinct. There is no unusual calcification or rarefaction. Examination done about two months later shows a definite increase in the size of the pelvic mass, which now rises out of the pelvis. The left kidney is seen to be tremendously increased in its degree of hydronephrosis. The left ureter can be followed only for a short distance. Examination of the stomach shows a hiatus hernia as described. The available films fail to reveal any definite intrinsic disease of the stomach itself. There is some suggestion of poor filling of the medial aspect of the duodenal loop, but I can make no further statement about that.

DR LEADBETTER: On viewing the x-ray films, I must say that the mass is larger and growing more rapidly than I had supposed from reading the record. It suggests that the lesion was a cystic tumor arising from the pelvic structures, probably the ovary. I have to retract my impression of recurrent carcinoma originating in the urinary tract.

CLINICAL DIAGNOSIS

Malignant ovarian cyst

DR LEADBETTER'S DIAGNOSES

Cystic ovarian tumor

Hydronephrosis and hydroureter, left

Chronic cystitis

ANATOMICAL DIAGNOSIS

Metastasis of papillary carcinoma of bladder to ovary

PATHOLOGICAL DISCUSSION

DR STURGIS: When this woman came into the hospital she had this tremendous tumor, filling the whole pelvis. It was somewhat fixed on the right side. We thought she had an ovarian cyst, probably malignant. This is why we operated, but I cannot explain the tripling in size during the short period of observation. We found that she had an ovarian cystic tumor definitely arising from the right ovary. It was very large, and in bringing it up we ruptured it. It was filled with dark, chocolate material, and was a papillary type of malignant growth in the ovary. The patient was seventy-one years old and had only one kidney, and because of the fear of spillage we did not do

more than remove the right ovary and closed her up. The uterus was tiny and atrophic. We believed that we were not justified in prolonging the operation for the sake of more accurate diagnosis.

DR MALLORY: The mass that reached the laboratory looked like an ordinary papillary serous cystadenoma of the ovary, on gross examination there was no question of what it was. On microscopical examination we found that the entire mass was lined with characteristic transitional epithelium, it looked exactly like a bladder papilloma, and I think, without doubt, it represented metastasis to the ovary, from a primary bladder or ureteral tumor. The tumor cells were those of a low-grade type of papillary carcinoma.

DR LEADBETTER: Why did the mass increase in size so rapidly? Because of hemorrhage?

DR MALLORY: The cyst contained a large amount of fluid, and there had been hemorrhage into it.

DR STURGIS: That is what we thought.

DR MEIGS: Could it not have started in a dermoid type of teratoma that contained a transitional type of epithelium rather than as a metastatic lesion?

DR MALLORY: I do not believe so. If I gave you a section of the wall of the ovary, I think you would, without hesitation, say that it was a characteristic bladder tumor. Whether or not the ovary was previously cystic, I do not know. It is possible that the metastasis occurred into an already cystic ovary. I cannot answer that.

DR MEIGS: Frequently tissue in the ovarian dermoid or teratoma resembles tissue from other parts of the body that can grow. We often see tumors that resemble the thyroid gland. We see intestinal or endocervical mucosa from which a pseudomucinous cystadenoma arises, so why cannot that kind of epithelium be found in a dermoid?

DR MALLORY: In theory any type of tissue may develop in a teratoma, in practice I have never seen an ovarian cyst with this type of lining. The only type of ovarian tumor containing transitional epithelium is a Brenner tumor, that has a different appearance.

DR MEIGS: And a Brenner tumor can also be associated with dermoid, can it not?

DR MALLORY: I have never heard of a Brenner tumor becoming malignant, however.

DR MEIGS: I have not either.

DR PARSONS: Was there any bone element?

DR MALLORY: We found none.

CASE 35062

PRESENTATION OF CASE

First admission. A fifty-three-year-old housewife was admitted to the hospital because of "asthma and exhaustion."

Before the age of forty the patient experienced occasional episodes of mild wheezing and dyspnea

with exertion. These were not particularly troublesome and were attributed to obesity. When she was forty she had rather severe "asthmatic attacks," which disappeared spontaneously after a few days. Since that time she had almost continuous year-around attacks, which could not be related to place or season. Three years before admission she was studied in another hospital, where she was said to have been allergic to goats, feathers and chocolate. She stated that the attacks became worse upon contact with these substances. Episodes of nervousness and tension also increased the symptoms, and because an active social life tended to aggravate her condition she had recently lived a rather secluded life. The last severe attack began about two months prior to admission at which time she was admitted to another hospital, where she gained some relief.

The patient's general health had "always been poor." An attack of rheumatic fever when she was seven was followed by sore throats three or four times yearly until the age of thirty-five, when a tonsillectomy was done. She had suffered frequent attacks of sinusitis, for which she was operated upon twice. During one period she took desiccated thyroid for obesity and developed marked tachycardia, nervousness and tremor. She had suffered bouts of diarrhea, lasting three or four days, coming on every three or four weeks, for the past four years. There was no history of chest pain or ankle edema.

Physical examination revealed a well developed and well nourished woman with slight asthmatic breathing. The neck veins were not distended, and the chest was symmetrical with increased anteroposterior diameters. There was moderate emphysema, with decreased fremitus and hyperresonance. There was questionable wheezing on the right side anteriorly. The point of maximal impulse was 1 cm beyond the midclavicular line, and a Grade I systolic murmur could be heard at the apex. The rhythm was normal, and the pulmonic second sound was not loud. The liver edge was felt 1 cm below the costal margin.

The temperature was 99.5°F, the pulse 115, and the respirations 24. The blood pressure was 140 systolic, 60 diastolic.

The urine was normal. The blood hemoglobin was 16 gm, the white-cell count was 8000, with 76 per cent neutrophils. The blood sugar was 116 mg, the nonprotein nitrogen 11 mg, and the total protein 4.4 gm per 100 cc. A roentgenogram of the chest disclosed fairly large lung fields, with some increased density posteriorly in the costophrenic angle. The diaphragm was low in position and showed some limitation of motion. The heart was in the upper limits of normal in size. Many scratch tests, including those for feathers and goats, were negative.

The patient continued to have dyspnea and spells of coughing. There was cyanosis of the lips and nail beds. On the eleventh hospital day the blood hemoglobin was 14.4 gm, and the total protein 5.02 gm per 100 cc, with an albumin-globulin ratio of 1.6. The blood sodium was 138.1 and the chloride 95 milliequiv per liter, the nonprotein nitrogen was 19 mg per 100 cc. On the seventeenth hospital day a "sore throat" developed, following which orthopnea and wheezing became worse. When sitting up in bed she was cyanotic, but upon lying flat much of this disappeared. The neck veins were distended, and there were rales in the chest. She was given several injections of mercurhydrin, after which she showed slow but steady improvement. She was discharged on the thirtieth hospital day.

Final admission (approximately three weeks later). In the interval the patient experienced little dyspnea or wheezing, although she remained in bed most of the time. One week before entry, however, she noticed swelling of the ankles and abdomen, although orthopnea and breathing were no worse. She was given several injections of mercurials to no avail.

On physical examination the patient breathed somewhat heavily but without audible wheeze. There was no cyanosis, the neck veins were distended. There were rales in both bases, and the heart findings were essentially the same as on the previous admission. The liver edge was palpated four fingerbreadths below the costal margin, with tenderness in the right upper quadrant. There was a +++ pitting edema of the ankles and ++ edema over the sacrum.

The temperature was 98°F, the pulse 90, and the respirations 20. The blood pressure was 120 systolic, 60 diastolic.

The urine gave a + test for albumin. The blood hemoglobin was 13 gm, the white-cell count was 9400, with 73 per cent neutrophils. The blood sugar was 148 mg, and the cholesterol 231 mg per 100 cc.

The patient's condition did not improve. She refused to eat a salt-free diet. A roentgenogram showed a suggestion of fluid in the right costophrenic sinus, and the heart shadow appeared slightly larger than before, the enlargement appearing to be chiefly in the region of the left ventricle. An electrocardiogram showed sinus tachycardia at a rate of 100, with a PR interval equal to 0.15 second. There was moderate right-axis deviation and a tendency toward low voltage in all limb leads. There was a low and upright T wave in Lead 1, depressed ST segments with diphasic T wave in Leads 2 and 3. The T waves were diphasic in Lead VR, low and upright in Lead VL, diphasic in VF and upright in V₁, V₄ and V₆. The ST segments were depressed in Lead VF.

On the fourth hospital day the blood sodium was 135.2 and the chloride 83 milliequiv per liter. Four days later the blood carbon dioxide was 44.1 milliequiv per liter. On the eleventh hospital day the red-cell count was 5,810,000, the hemoglobin 13.6 gm and the pH 7.35. The patient became progressively more cyanotic but with little orthopnea. There were rales in the right base but normal breath sounds. There was +++ edema of the lower extremities, and ++ edema over the abdominal wall. The abdomen was distended, and shifting dullness was present. On the sixteenth hospital day the serum protein was 6 gm per 100 cc, and the potassium 5.4, the sodium 138.8 and the chloride 83 milliequiv per liter. She was given mercurial diuretics intermittently, with irregular response. Oxygen relieved much of the cyanosis. During the following several weeks periods of improvement alternated with periods of relapse, although the course was progressively downhill. On the forty-fifth hospital day the patient began fibrillating, the temperature, pulse and respirations rose, and two days later she died.

DIFFERENTIAL DIAGNOSIS

DR J. EVARTS GREENE. This patient is said to have had occasional episodes of mild asthma or at least mild wheezing and dyspnea on exertion before the age of forty. There is no record of such symptoms without exertion, they were attributed to obesity, but it is possible that they were due to early emphysema or low-grade chronic bronchitis. When she was forty she had what was described as a severe asthmatic attack, and thereafter she had asthma the year round without relation to place or season. Forty years of age is the time, as Dr Rackemann has frequently emphasized, when intrinsic asthma begins to be much more frequently noted than extrinsic. I think the fact that she had her symptoms all year round, without relation to season or place, but increased by nervous tension, is in favor of a diagnosis of intrinsic asthma. She may have had minor allergies, but they certainly did not play an important part in her final illness. Her general health was always poor. She had early rheumatic fever, many sore throats and attacks of sinusitis. I cannot relate these conditions to the complaints that led to death. She is also said to have suffered from repeated diarrhea, apparently quite frequently, every three or four weeks.

I would like to ask if any stool specimens were examined for amebic cysts.

DR FRANCIS M. RACKEMANN. No.

DR GREENE. If the patient had amebic colitis, it could hardly have had any bearing on what happened later. On physical examination she had signs of emphysema and mild asthma. There was questionable wheezing on the right side. The liver edge was felt 1 cm below the costal margin. The blood

pressure was 140 systolic, 60 diastolic — certainly not a low pressure

The laboratory findings, except for moderately low total protein, do not seem remarkable. X-ray examination is said to have shown fairly large lung fields, with increased density posteriorly in the costophrenic angle. May we see the films?

DR STANLEY M. WYMAN: The films taken on the first examination show the density described in the posterior costophrenic sinuses, which I believe represents a small quantity of fluid in both pleural spaces. Increase in the anteroposterior chest diameter is quite well shown. The lung fields themselves seem rather large and somewhat bright for a patient of this size. The heart shadow is at the upper limits of normal, without definite characteristic configuration, however. I think we should add that the hilar vascular shadows are increased in prominence, and the proximal portions of the pulmonary artery in both lung fields are somewhat engorged. I cannot see any definite localized pulmonary disease, however.

Examination two months later shows a definite but small quantity of fluid in the right costophrenic sinus and possibly on the left. The heart shadow may be a little larger. This is not a very conclusive finding. The third examination has not, so far as I can see, changed materially. I think the statement that the left ventricle appeared to be large is wrong; I think this simply emphasizes to us once again that we cannot differentiate well left ventricular from right ventricular enlargement in the presence of engorged pulmonary vascular shadows. Right ventricular enlargement is more consistent with this picture.

DR GREENE: There is no evidence of pulmonary fibrosis?

DR WYMAN: We looked carefully for diffuse pulmonary fibrosis because we thought that this patient had cor pulmonale but were unable to be certain of diffuse fibrosis. I know that it can be completely missed on x-ray examination, however.

DR GREENE: Did you find anything suggesting calcification of the pericardium?

DR WYMAN: No, neither fluoroscopically nor on the films.

DR GREENE: The skin tests done here were apparently negative. The patient continued in the first hospitalization to have dyspnea and coughing, with cyanosis.

I do not think the blood chemical findings, except for the total protein, were significantly altered. On the seventeenth day the patient was said to have developed a "sore throat." I am not sure whether that means that no one could see an inflammatory process. At least orthopnea and wheezing became worse.

"While sitting in bed she was cyanotic, but upon lying flat much of this disappeared." I do not know what that statement signifies. I have seen an occa-

sional patient with emphysema who stated that he was a good deal more comfortable lying down than sitting up. Usually, such patients merely state that they are not more uncomfortable lying down than sitting up. On the other hand, the patient is said to have had orthopnea at this point, but why the cyanosis disappeared on lying down, I cannot say. During the interval between hospitalizations, swelling of the ankles progressively increased. On the second hospital admission the liver was markedly enlarged, and again the neck veins were distended but there was no cyanosis.

DR RACKEMANN: I do not think that is correct. As I recall, there was cyanosis all the time.

DR GREENE: The blood sugar was 148 mg per 100 cc, that is an isolated finding, and I am tempted to disregard it. The heart was more enlarged, and electrocardiographic findings seem consistent with right-sided failure. I would be interested in hearing the cardiologists say a word about the unipolar leads.

DR CONGER WILLIAMS: They do not add a thing, I have been over them, and they do not help at all.

DR GREENE: The carbon dioxide of 44 milliequiv per liter — a somewhat elevated figure — is consistent with emphysema. Patients with emphysema are supposed to have difficulty in eliminating carbon dioxide. During the second admission the red-cell count rose, consistent with passive congestion and emphysema. There was no definite acidosis, and the potassium was said to have been elevated. That is sometimes found in allergic episodes. I do not believe an acute allergic episode was involved at this stage of the game. It seems that the patient was going downhill slowly, with right-sided heart failure, and that she died for that reason.

In discussing the possible diagnoses we can dismiss the possibility of such conditions as nephrosis, amyloidosis and cirrhosis of the liver, which might cause swelling of the legs and abdomen, because they would not account for cyanosis or dyspnea. I think that asthma and pulmonary emphysema, followed by cor pulmonale, with right-sided heart failure and chronic passive congestion, would give a satisfactory explanation of this patient's illness. There is a possibility also, although it seems unlikely, that she had chronic constrictive pericarditis, which certainly could have caused the cyanosis and the swelling of the extremities and abdomen. However, as evidence against this, the patient apparently improved on mercurial diuretics, at least temporarily, she did not show any sign by x-ray study of pericardial thickening, and there was no history of antecedent illness to account for it. Ajerza's disease must be considered as a possibility, but I do not think we have enough definite data to make that diagnosis. Periarteritis nodosa is occasionally associated with asthma, but I cannot see that we have any definite reason to make a diagnosis of that condition. So I come back to my

The patient continued to have dyspnea and spells of coughing. There was cyanosis of the lips and nail beds. On the eleventh hospital day the blood hemoglobin was 14.4 gm, and the total protein 5.02 gm per 100 cc, with an albumin-globulin ratio of 1.6. The blood sodium was 138.1 and the chloride 95 milliequiv per liter, the nonprotein nitrogen was 19 mg per 100 cc. On the seventeenth hospital day a "sore throat" developed, following which orthopnea and wheezing became worse. When sitting up in bed she was cyanotic, but upon lying flat much of this disappeared. The neck veins were distended, and there were rales in the chest. She was given several injections of mercurhydrin, after which she showed slow but steady improvement. She was discharged on the thirtieth hospital day.

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The temperature was 98°F, the pulse 90, and the respirations 20. The blood pressure was 120 systolic, 60 diastolic.

The urine gave a + test for albumin. The blood hemoglobin was 13 gm, the white-cell count was 9400, with 73 per cent neutrophils. The blood sugar was 148 mg, and the cholesterol 231 mg per 100 cc.

The patient's condition did not improve. She refused to eat a salt-free diet. A roentgenogram showed a suggestion of fluid in the right costophrenic sinus, and the heart shadow appeared slightly larger than before, the enlargement appearing to be chiefly in the region of the left ventricle. An electrocardiogram showed sinus tachycardia at a rate of 100, with a PR interval equal to 0.15 second. There was moderate right-axis deviation and a tendency toward low voltage in all limb leads. There was a low and upright T wave in Lead 1, depressed ST segments with diphasic T wave in Leads 2 and 3. The T waves were diphasic in Lead VR, low and upright in Lead VL, diphasic in VF and upright in V₁, V₄ and V. The ST segments were depressed in Lead VF.

On the fourth hospital day the blood sodium was 135.2 and the chloride 83 milliequiv per liter. Four days later the blood carbon dioxide was 44.1 milliequiv per liter. On the eleventh hospital day the red-cell count was 5,810,000, the hemoglobin 13.6 gm and the pH 7.35. The patient became progressively more cyanotic but with little orthopnea. There were rales in the right base but normal breath sounds. There was +++ edema of the lower extremities, and ++ edema over the abdominal wall. The abdomen was distended, and shifting dullness was present. On the sixteenth hospital day the serum protein was 6 gm per 100 cc, and the potassium 5.4, the sodium 138.8 and the chloride 83 milliequiv per liter. She was given mercurial diuretics intermittently, with irregular response. Oxygen relieved much of the cyanosis. During the following several weeks periods of improvement alternated with periods of relapse, although the course was progressively downhill. On the forty-fifth hospital day the patient began fibrillating, the temperature, pulse and respirations rose, and two days later she died.

DIFFERENTIAL DIAGNOSIS

DR J EVARTS GREENE. This patient is said to have had occasional episodes of mild asthma or at least mild wheezing and dyspnea on exertion before the age of forty. There is no record of such symptoms without exertion, they were attributed to obesity, but it is possible that they were due to early emphysema or low-grade chronic bronchitis. When she was forty she had what was described as a severe asthmatic attack, and thereafter she had asthma the year round without relation to place or season. Forty years of age is the time, as Dr Rackemann has frequently emphasized, when intrinsic asthma begins to be much more frequently noted than extrinsic. I think the fact that she had her symptoms all year round, without relation to season or place, but increased by nervous tension, is in favor of a diagnosis of intrinsic asthma. She may have had minor allergies, but they certainly did not play an important part in her final illness. Her general health was always poor. She had early rheumatic fever, many sore throats and attacks of sinusitis. I cannot relate these conditions to the complaints that led to death. She is also said to have suffered from repeated diarrhea, apparently quite frequently, every three or four weeks.

I would like to ask if any stool specimens were examined for amebic cysts.

DR FRANCIS M RACKEMANN. No.

DR GREENE. If the patient had amebic colitis, it could hardly have had any bearing on what happened later. On physical examination she had signs of emphysema and mild asthma. There was questionable wheezing on the right side. The liver edge was felt 1 cm below the costal margin. The blood

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MEDICAL MONOPOLISTS

WHILE physicians argue among themselves over the most effective method by which their relations with the public can be improved, the lay public is being enlightened in a number of ways. One of the most recent is an article by J. D. Ratchiff in the *Woman's Home Companion* for October, 1948, that has been announced in full-page advertisements in various newspapers. With a foreword by Dr. Allen O. Whipple, former president of the American Board of Surgery, it exposes the "medical monopolists" who keep brilliant young doctors out of hospital staffs for fear of competition. For human interest it tells the story of "brilliant young Dr. Jim

Smith — straight A's" — and how he was "barred from practice in hundreds of communities by men with a fraction of his skill." The punch line is that so long as this deplorable situation goes unremedied, the community "will continue to get 1920 medicine for 1948 ills."

No exception can be taken to the article itself. Were it published to be read only by the medical profession it would amount simply to a necessary display of dirty linen in urgent need of washing. Directed to the lay public, however, and accompanied by an exhortation to "civic-minded individuals and organizations" to send for free reprints and then to "bring public opinion to bear," it becomes a subtle piece of propaganda in favor of state medicine. Its most effective feature is its omission of any reference to state medicine.

For who can doubt the direction in which such civic-minded public opinion would be directed? And on whom would the pressure be exerted? It would be "brought to bear" on the congressmen who are already considering bills for governmental control of the practice of medicine.

But is that the way to remedy this admittedly deplorable situation? By what laws have morals ever been successfully dictated? Deplorable economic and political situations exist about which the individual physician can do little or nothing — the high cost of medical care, the high price of medical education and the shortage of hospital beds, to mention only a few — but this "medical monopolist" situation is one piece of dirty linen that the medical profession should be able to wash for itself because it is essentially a moral situation. That the leaders in the profession are aware of its existence and are eager to put a stop to it is evident in the presidential address delivered last fall before the New England Surgical Society and published elsewhere in this issue of the *Journal*. Wherever it may exist it is a cynical betrayal of the public confidence, a brazen violation of the Hippocratic oath and a selfish denial of the basic purpose of the whole medical profession. A better punch line would have been wash day is here — if you doctors don't want to be taken to the cleaners by force, start washing!

first diagnosis of asthma, emphysema, cor pulmonale and right-sided heart failure

DR RACKEMANN We had quite a time with this patient. I do not think the history gives quite a true picture of what was going on. The attack that she had at the outside hospital before she came in here was quite obviously asthma. She came in here three months before she died. The low serum protein on the first admission was quite striking. The connection of this finding with her other symptoms was hard to determine, and what caused the cyanosis was hard to say. There was some asthma, — a little shortness of breath, — but it was not striking at that time. There was no evidence that I could see of any strain on the right side of the heart. However, the consultants, Drs Bland and Williams, showed that I was wrong — that the cyanosis could be interpreted on the basis of right-sided heart failure. She went home in fair shape. Three weeks later she came in again, and the picture was entirely different. The cyanosis was still present, but she had a full-blown picture of right-sided heart failure, with severe pitting edema of the extremities, fluid in the abdomen and soft, pitting edema of the abdominal wall. That bothered us a good deal. Why did she have edema? Why did she not improve with digitalis and mercurial and other diuretics? It was all very puzzling. The story of asthma did not seem severe enough to produce the strain on the right side of the heart, considering that so many people have the same story with no such terminal findings. Then, as we went on, it became clear that she could not get rid of the excessive carbon dioxide. The heart seemed normal, the pulse was regular, the rate being elevated to 100 or sometimes 110. Days and weeks went by, and very little change occurred in the *status quo*. Except for the continuous edema, the heart seemed to function reasonably well. So then we began to think about other reasons for obstruction of the blood flow from the right side of the heart, and that led us to lean toward the diagnosis of Ayerza's disease.

DR WILLIAMS I have little to add. I was interested in one thing — namely, that in several reported series of patients with cor pulmonale secondary to pulmonary asthma the patients had been entirely or predominantly of the male sex. I think it is a little unusual for someone to develop pulmonary fibrosis, or whatever one chooses to call this syndrome, in such an apparently short time on the basis of asthma alone. I do not see any other explanation for it, however.

DR DONALD S KING In the past we have not had to have changes in blood vessels, emphysema occurred alone with this much right-sided failure

CLINICAL DIAGNOSES

Cor pulmonale
Pulmonary endarteritis
Ayerza's disease

DR GREENE'S DIAGNOSES

Bronchial asthma
Pulmonary emphysema
Chronic cor pulmonale
Right-sided heart failure

ANATOMICAL DIAGNOSES

Pulmonary emphysema
Pulmonary arteriosclerosis
Cor pulmonale
Terminal thrombosis of pulmonary arterioles
Acute central necrosis of liver
Adenocarcinoma of thyroid gland

PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY Autopsy showed voluminous emphysematous lungs, with large blebs in them. The pulmonary vessels demonstrated numerous atheromatous plaques, and the small pulmonary arteries and arterioles contained thrombi very diffusely and extensively throughout the lung. These thrombi were rather friable and slightly adherent to the vessel wall. At the time of autopsy we thought they might show early organization. Microscopical sections failed to confirm that entirely. The thrombi must have been of quite recent origin — I should think certainly less than a week's duration, perhaps three to five days — so they can be regarded only as a terminal event. The heart weighed 420 gm, and the right ventricle was 9 mm in thickness, a marked grade of cor pulmonale. The liver showed an extreme degree of passive congestion, with acute terminal central necrosis, which, I think, was perhaps of the same duration as the acute process in the pulmonary arteries. There was an incidental finding — a markedly nodular thyroid gland, and one of the nodules showed early carcinomatosis. That had nothing to do with the symptomatology, however. From the anatomic point of view, the only diagnoses are emphysema, pulmonary arteriosclerosis, cor pulmonale and a terminal episode of acute thrombosis of the small pulmonary arteries. The picture was not what one ordinarily calls Ayerza's disease — long-standing apparently primary disease in the pulmonary arteries.

sity hospital. In New England the same joining of interests has taken place, but we do not have university hospitals as such, preferring to enjoy the obvious advantages without merging the identity of either institution into the other. Our arrangement calls for a little more understanding on the part of all concerned, but this is only a greater stimulus to co-operation and recognition of the common cause. As these centripetal forces continue, what are becoming known as medical centers are formed. In a modern medical center there appear to be not two, but three major interests: medical education and medical care find themselves in the presence of a third party, medical research. How to make elbow room for this new and essential interest has already become a problem in many centers.

At the New England Medical Center the solution of the problem was dedicated on November 11, 1948, at the formal opening of the Ziskind Research Laboratories. In a seven-story building 24,000 square feet of floor space are already equipped and in use, another 36,000 feet are ready to be equipped in the near future, and a total capacity of 96,000 square feet is available in the potential capacity of the building as a whole. The two floors now in use are connected by a bridge with the Joseph H. Pratt Diagnostic Hospital, which in turn is connected with the other units of the Center.

Mr. Jacob Ziskind's generosity has thus solved the problem of adequate physical facilities for research at this center for many years to come. But, as is so often the case and as was pointed out at the dedicatory exercises, the solution of one problem creates another, how may the research activities best fit themselves into the programs of medical care and medical education already underway? In discussing the necessity for careful integration of these elements it was stated that an effort would be made to have the staff fall into three broad categories: bedside clinicians, basic research scientists and a group who might be termed "clinical scientists." The clinical scientist would attempt to be conversant with the problems both of the bedside and of the laboratory. The center would then have to rely for its fullest development on the combined efforts of these three groups. With such a staff it is hoped t

laboratory to the bedside can develop. So the evolutionary processes go on.

POSTGRADUATE LECTURE COURSE

WITH the fourth annual postgraduate lecture course in general medicine impending, it is rapidly becoming a midwinter tradition to give it the usual journalistic introduction. There seems to be no reason why this course should not take equal rank with the better known of the various winter carnivals, perhaps even with New Orleans's famous Mardi Gras—less spectacular but still more instructive.

Arranged by the efficient and far-sighted Committee on Postgraduate Education of the Massachusetts Medical Society, the course will again be given in Sanders Theater, Harvard University, Cambridge. It will run, as usual, on Mondays from 6 00 to 9 00 and on Wednesdays from 4 00 to 6 00 p m, beginning this year on Monday, March 7, and closing on Wednesday, April 27. An outline of the program is printed elsewhere in this issue of the *Journal*, and the full program will be published shortly.

A feature of the 1949 program will be the discussions planned for March 7, built around the subject of "A Positive Program for the Health of the Public." This program, on the "hottest" subject in medicine today, will be under the joint chairmanship of Dr. James S. Simmons, dean and professor of public health at the Harvard School of Public Health, and Dr. John F. Conlin, director of medical information and education of the Massachusetts Medical Society.

Participating will be Dr. Hugh R. Leavell on "Local Health Departments," Dr. Samuel B. Kirkwood on "Maternal and Child Health," Dr. Stuart S. Stevenson on "School Health," and Dr. Albert O. Seeler on "Industrial Health." All the speakers are from the Harvard School of Public Health.

The course is free to all physicians residing in New England, regardless of membership in any medical society. Those who wish to register immediately for the course should do so by writing to the Postgraduate Lecture Course Committee, Massachusetts Medical Society, 8 Fenway, Boston.

THE THERAPEUTIC ROLE OF THE KEMPNER DIET

DIETARY restriction of one sort or another has been utilized in the treatment of hypertensive disease for many years. In 1945 Kempner¹ presented the details of his commendably aggressive approach to the dietary treatment of this group of diseases and thereby stirred up a great deal of comment, both medical and lay. Kempner's own therapeutic results are little short of miraculous and have justifiably impressed numerous competent and critical observers who have visited the North Carolina clinic. Investigators other than Kempner have obtained favorable, but not miraculous, results in most cases, and the chief difficulty seems to center around the extreme monotony of the diet. Most physicians lack the extraordinarily persuasive powers required to keep a patient eating rice and certain types of fruit for weeks, months or even indefinitely. The usual result is that the patient fails to eat all the food presented to him and, not infrequently, finally rejects the diet altogether.

Kempner's claim that patients following his regimen remain in nitrogen balance is adequately refuted by recent balance studies.² Regarding maintenance of weight on the Kempner diet there is further disagreement between Kempner and other workers. Kempner finds that patients receiving the diet lose weight initially but after some weeks the weight becomes stable and all is well—in fact, so well that the diet can often be modified slightly. He attributes the initial loss of weight to loss of fluid. It has proved very difficult for other investigators to confirm or deny these claims, mainly because so many patients cannot conform to the rigid requirements of the Kempner regimen over long periods. It seems clear, however, that patients receiving the Kempner regimen in clinics other than Kempner's own lose not only fluid but also body tissue. The diet, as it usually works out in practice, is a specialized sort of starvation ration, and the contention that it is adequate in calories and protein needs modification.

It is entirely possible that the tendency for patients on the Kempner regimen to eat less than the stipulated amounts of rice and fruit can be used to advantage in certain types of cardiac disease with

failure. Salt restriction in such patients is unquestionably highly important. Reduction in weight over and above that due to fluid accumulation is crucial in many obese patients with cardiac failure. Heretofore the patient has been offered a low calorie diet, which often supplies 800 calories or less, to achieve loss of body tissue. He has been implored and cajoled not to eat more than the allowed amount, in spite of which he often reaches a point where he secretly takes extra food and the physician cannot understand why the patient's weight remains too high. The psychologic, as well as the physiologic, advantages of the Kempner regimen in this situation seem not to have been appreciated. Using the rice-fruit diet, the physician, instead of pleading with his patient to eat less, actually has to urge the patient to eat all the food given him. The very low salt intake, a difficult feature to control on any sort of hospital diet other than that devised by Kempner, helps to rid the patient of excessive fluid, and concurrently, the usual inability to maintain the caloric intake allowed by the Kempner regimen causes a reduction in body fat and protein. Practically speaking, there probably is no more effective diet for obese decompensated cardiac patients.

Although the Kempner regimen is certainly not the final answer in the treatment of hypertensive disease, it is an important development in the search for a practical and uniformly successful method of treating the disorder. Furthermore, it may well find a permanent place in the treatment of some types of congestive cardiac failure and even in uncomplicated obesity.

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- 2 Schwartz, W B and Merlis J K. Nitrogen balance studies on Kempner rice diet. *J Clin Investigation* 27: 406-411 1948

THE ZISKIND RESEARCH LABORATORIES

DURING the past quarter century the evolution of medical knowledge has brought into action a centripetal force that crowds together groups of interests and activities formerly carried on as separate endeavors. Medical education and medical care were the first to merge, and their common interests have produced in many parts of the nation a type of institution aptly described as the univer-

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MISCELLANY

INSURANCE FOR ALCOHOLICS

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HAROFÉ HAFRI

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In publishing *Harofé Hafri* semiannually, the editors have met the need for a medical journal written in Hebrew, with English summaries, thus aiding greatly in the advance and development of Hebrew medical literature.

AMERICAN HEART ASSOCIATION

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CORRESPONDENCE

REGARDING EXTRARENAL AZOTEMIA

To the Editor: I have read with much interest the article by Appel and Townsend entitled "Extrarenal Azotemia: Report of a severe case with recovery" in the January 20 issue of the *Journal*. The case reported therein would, I think, fit very nicely a diagnosis of lower-nephron nephrosis with spontaneous recovery. More specifically, the patient had severe oliguria for about ten days, followed by a diuresis (he was excreting over a liter of urine by the second hospital day); he had a marked azotemia, and examination of the urine showed red cells, white cells and casts in the sediment. The vomiting (with loss of hydrochloric acid) and the voluntary reduction of fluid intake during the oliguric period may well account for the alkalosis and for the failure to form edema respectively. The case would fit quite well into the series of lower-nephron nephroses with spontaneous recovery reported by Strauss in the November 4 issue of the *Journal*.

WALTER HOLLANDER, JR.

338 Vanderbilt Hall
Longwood Avenue
Boston 15, Massachusetts

Mr. Hollander's letter was referred to Dr. James H. Townsend, senior author of the article in question, who made the following reply:

To the Editor: The point raised by Mr. Hollander is a good one. In the absence of any histologic examination, of course, we cannot say whether there may have been morphologic changes in the kidney. Because of the very slight changes in the urine and the promptness of the recovery following administration of salt and water we believed that there was little if any actual disease in the kidney.

The distinction between "extrarenal azotemia" and lower-nephron nephrosis, I think, is very largely an academic one. In this case there had been no condition leading to shock or severe anoxia or any other dramatic episode to cause a nephrosis. We chose to call the disease extrarenal azotemia. If Mr. Hollander chooses to call it lower-nephron nephrosis, I should not object. The point is that this patient presented a severe picture resembling uremia that might well have been fatal and was very easily corrected by the simple administration of salt and water. He showed no evidence of any previous or permanent renal damage.

I have recently seen a somewhat similar case in another hospital that proved fatal and in which the kidneys showed no demonstrable lesion whatever. The patient was a catatonic schizophrenic who became extremely overactive and dehydrated and went into shock with azotemia and died.

JAMES H. TOWNSEND, M.D.

Mount Auburn Hospital
Cambridge, Massachusetts

NOTICES

ANNOUNCEMENTS

Dr. Sidney S. Gellis announces the removal of his office from 319 Longwood Avenue, Boston, to the Children's Hospital, 300 Longwood Avenue, Boston, for the practice of pediatrics.

Dr. Harold I. Shuman announces the removal of his office from 433 Beacon Street, Boston, to 92 Broadway, Taunton, for the practice of pediatrics.

Dr. Richard H. Wright announces the opening of his office for the practice of internal medicine at 1180 Beacon Street, Brookline.

SOUTH END MEDICAL CLUB

A regular luncheon meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston on Tuesday, February 15, at 12 noon. Dr. George W. Thorn will speak on the subject "Screening Tests for Adrenal Insufficiency."

All physicians are cordially invited to attend.

BOSTON MEDICAL LIBRARY

PERSONNEL

Mr Charles C Colby, III, joined the Library staff the first of the year as reference librarian, succeeding Miss Catherine Binderup. Mr Colby has an excellent background for the position, with the degree of A B from Harvard University in the field of biology (1943) and S B from Simmons College Library School (1947). He has had one year of a premedical course at Yale University and half a year in the basic medical sciences at Harvard Medical School. From the time of his graduation from Simmons College in June, 1947, until the end of 1948 he was employed as a cataloger at the Army Medical Library in Washington.

EXHIBITS

Concurrently with the meeting of the American Numismatic Society held in Boston in 1948, an exhibit of medals and coins of medical significance dating from the Roman period to modern times was placed in the rotunda at the Library. Through the courtesy of Dr Elliott P Joslin, the two diabetes medals awarded to survivors of the disease over long periods by the George F Baker Clinic were also displayed. Dr Paul Mueller, who recently received the Nobel prize for his discovery of DDT, was the subject of another exhibit, which included his portrait, his original article on his investigations, a sample of the insecticide and other material.

IMPORTANT ACCESSIONS

The Library is interested in the work of René Descartes, especially in the fields of knowledge related to medicine. The Library recently had the opportunity of obtaining a good, small collection of his publications, including the definitive edition of his collected works, published under the auspices of the minister of public instruction of the French Republic in twelve volumes (Paris, 1897-1910). This edition was reserved primarily for French libraries and institutions and is consequently a scarce set outside France. Unfortunately, it is printed on very poor paper that will not survive the ravages of use and time. There are also the *Opera philosophica* (Frankfurt, 1792-1797) in three volumes, and the *Oeuvres*, published by Victor Cousin (Paris, 1824-1826) in eleven volumes and an atlas. The Library already owned three early editions of *De homine*.

The reference division has been enriched by the acquisition of the Edwards reprint of the British Museum Catalogue, an essential tool for medical bibliographical research.

NEW PERIODICALS

The following sets have been added to the periodical division

American Journal of Orthopsychiatry (Menasha)
Vol 8 to date. The Library needs Vol 1 to 7 to complete this important set.
Folia cardiologica (Milan)
Helvetica medica acta (Basel)
Revista Espanola de cirurgia (Madrid)
Revue d'hématologie (Paris)
Revista do Instituto Adolfo Lutz (São Paulo)

The Library has subscribed to the complete series of the *Excerpta medica*.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

END OF DISTRIBUTION OF DRIED PLASMA BY RED CROSS

Dr Harry Kleinschmidt, director of health services of the North Atlantic Area of the American National Red Cross, has notified Dr Vlado A. Getting, commissioner of health for Massachusetts, that no further shipments of surplus dried plasma will be made after December 31, 1948. The supply of dried plasma turned over to the Red Cross after VJ Day is now reported to be so low that nationwide distribution cannot be continued. Dr Kleinschmidt expressed the hope that sufficient whole blood would be collected by the National Red Cross Blood Program to provide whole blood, plasma and fractions for the entire country.

Distribution of this plasma in Massachusetts during the past two years has been effected through the Division of Biologic Laboratories, 375 South Street, Jamaica Plain, Boston. At the present rate of distribution, the residual supply on hand at the Jamaica Plain depot will last until April 1, 1949. Hospitals are urged to conserve the plasma as much as possible until the Red Cross Blood Program is able to replace it with new material.

SEROLOGIC TESTS ON CONVALESCENTS FROM INFLUENZA

The Department is co-operating with the National Influenza Information Center by attempting to determine the type of influenza virus present whenever the disease becomes prevalent. The Department is asking the co-operation of physicians in all parts of the Commonwealth in sending in acute and convalescent blood specimens on a small representative sample of the most suspicious cases occurring in an area where the disease appears to be prevalent.

Attention is called to the fact that this is *not a diagnostic test*. Information about the type will not become available until the patient is in the *convalescent stage*.

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CORRESPONDENCE

REGARDING EXTRARENAL AZOTEMIA

To the Editor: I have read with much interest the article by Appel and Townsend entitled "Extrarenal Azotemia: Report of a severe case with recovery" in the January 20 issue of the *Journal*. The case reported therein would, I think, fit very nicely a diagnosis of lower-nephron nephrosis with spontaneous recovery. More specifically, the patient had severe oliguria for about ten days, followed by a diuresis (he was excreting over a liter of urine by the second hospital day), he had a marked azotemia, and examination of the urine showed red cells, white cells and casts in the sediment. The vomiting (with loss of hydrochloric acid) and the voluntary reduction of fluid intake during the oliguric period may well account for the alkalosis and for the failure to form edema respectively. The case would fit quite well into the series of lower-nephron nephroses with spontaneous recovery reported by Strauss in the November 4 issue of the *Journal*.

WALTER HOLLANDER, JR.

338 Vanderbilt Hall
Longwood Avenue
Boston 15, Massachusetts

Mr. Hollander's letter was referred to Dr. James H. Townsend, senior author of the article in question, who made the following reply:

To the Editor: The point raised by Mr. Hollander is a good one. In the absence of any histologic examination, of course, we cannot say whether there may have been morphologic changes in the kidney. Because of the very slight changes in the urine and the promptness of the recovery following administration of salt and water we believed that there was little if any actual disease in the kidney.

The distinction between "extrarenal azotemia" and "lower-nephron nephrosis," I think, is very largely an academic one. In this case there had been no condition leading to shock or severe anoxia or any other dramatic episode to cause a nephrosis. We chose to call the disease extrarenal azotemia. If Mr. Hollander chooses to call it lower-nephron nephrosis, I should not object. The point is that this patient presented a severe picture resembling uremia that might well have been fatal and was very easily corrected by the simple administration of salt and water. He showed no evidence of any previous or permanent renal damage.

I have recently seen a somewhat similar case in another hospital that proved fatal and in which the kidneys showed no demonstrable lesion whatever. The patient was a catatonic schizophrenic who became extremely overactive and dehydrated and went into shock with azotemia and died.

JAMES H. TOWNSEND, M.D.

Mount Auburn Hospital
Cambridge, Massachusetts

NOTICES

ANNOUNCEMENTS

Dr. Sidney S. Gellis announces the removal of his office from 319 Longwood Avenue, Boston, to the Children's Hospital, 300 Longwood Avenue, Boston, for the practice of pediatrics.

Dr. Harold I. Shuman announces the removal of his office from 483 Beacon Street, Boston, to 92 Broadway, Taunton, for the practice of pediatrics.

Dr. Richard H. Wright announces the opening of his office for the practice of internal medicine at 1180 Beacon Street, Brookline.

SOUTH END MEDICAL CLUB

A regular luncheon meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, February 15, at 12 noon. Dr. George W. Thorn will speak on the subject "Screening Tests for Adrenal Insufficiency."

All physicians are cordially invited to attend.

NORFOLK DISTRICT MEDICAL SOCIETY

A meeting of the Norfolk District Medical Society will be held at the Boston Medical Library, 8 Fenway, Boston, on Wednesday, February 23, at 8 p.m. The scientific program, entitled "Symposium on Thromboembolic Disease," will be as follows:

Physiologic Aspects of Intravascular Thrombosis William C. Moloney, M.D.

Clinical Aspects of Anticoagulant Therapy James A. Evans, M.D.

Surgical Aspects of Thromboembolic Disease E. Everett O'Neil, M.D.

All physicians are invited

NORFOLK DISTRICT WOMEN'S AUXILIARY

The Women's Auxiliary of the Norfolk District Medical Society will meet in the State Suite at the Copley Plaza Hotel, Boston, on February 28, at 2:30 p.m.

BOSTON SURGICAL SOCIETY

The monthly clinical meeting of the Boston Surgical Society will be held in co-operation with the Staff of the Paraplegia Service of Cushing Veterans Administration Hospital, Framingham, Massachusetts, on Friday, February 25. A symposium entitled "Some Aspects of Paraplegic Care" will be presented.

PROGRAM

Recreation Hall (9:30 a.m.)

Welcome and Introduction Drs. R. R. Gasser and H. S. Talbot

The Immediate Care of Patients Following Spinal-Cord Injury Dr. Donald Munro

Some General Metabolic and Hygienic Problems Dr. Joseph W. O'Neil

The Major Urologic Considerations Dr. Arthur Bassell
The Problem of Pain Drs. John H. Van Landingham and John T. O'Neil

Intermission — Visit to Ambulation Clinic (11:00 a.m.)

Ward (11:30 a.m.)

Demonstration of Tidal Drainage and Cystometry Dr. Melvin K. Lyons

The Surgical Treatment of Pressure Sores Dr. Robert T. Steinsieck

Discussion (12:00 m. to 12:30 p.m.)

For those who wish to remain, lunch will be served (60 cents) and there will be informal tours of the paraplegic wards and related departments after lunch. To facilitate adequate arrangements, guests who desire lunch should so notify Dr. H. S. Talbot, Cushing Veterans Administration Hospital, Framingham, Massachusetts, not later than Tuesday, February 22.

POSTGRADUATE INSTITUTE OF
PHILADELPHIA COUNTY MEDICAL SOCIETY

The Philadelphia County Medical Society will hold its Thirteenth Annual Postgraduate Institute at the Bellevue-Stratford Hotel, Philadelphia, from April 5-8. The program has again been arranged on the basis of symposia, and the following subjects will be covered: diseases of the circulatory system, common conditions in the oral cavity, diabetes, anterior poliomyelitis, blood dyscrasias, diseases of the kidney, miscellaneous problems, pain, industrial medical and surgical problems, common obstetric problems, problems of infancy and childhood, eye, ear, nose and throat, gastrointestinal problems and vaginal discharge (causes and treatment).

There will be the usual number of high-grade technical exhibits.

The admission fee for the entire institute is \$5.00. Programs will be available very shortly.

For further details application should be made to Gilson Colby Engel, M.D., Director, 301 South 21st Street, Philadelphia 3, Pennsylvania.

AMERICAN BOARD OF OPHTHALMOLOGY

The American Board of Ophthalmology does not evaluate, approve or disapprove any ophthalmic residency toward fulfilling the requirements for candidates for board examination. Any candidate who qualifies for the board examination and completes the prerequisites as outlined in the booklet of information will be accepted. A copy of this booklet can be obtained from the secretary of the American Board of Ophthalmology, 56 Ivie Road, Cape Cottage, Maine.

AMERICAN ACADEMY OF GENERAL PRACTICE

Application blanks for membership in the American Academy of General Practice may be obtained from the secretary of the Massachusetts chapter, Dr. James G. Simmons, of Fitchburg.

INTERNATIONAL AND FOURTH AMERICAN
CONGRESS ON OBSTETRICS AND GYNECOLOGY

The meeting of the International and Fourth American Congress on Obstetrics and Gynecology will be held at the Hotel Statler (formerly, Hotel Pennsylvania), New York City, on May 14 to 19, 1950, under the sponsorship of the American Committee on Maternal Welfare.

The preliminary program for the scientific sessions will include morning meetings, Monday through Friday, May 15 to 19, of general sessions each devoted to one of the following five topics: physiology of human reproduction, pathology of human reproduction, social and economic problems, neoplastic diseases of the female reproductive system, and obstetric and gynecologic procedures. The afternoons will be given over to meetings of various groups represented at the Congress, including nurses, nurse midwives, hospital administrators, educators, practicing physicians, investigators in special fields and public-health doctors and nurses.

Applications for space in the scientific exhibit or for time on the motion-picture program should be submitted to the chairman in charge of these activities on official application blanks obtainable from the business office of the International Congress at 24 West Ohio Street, Chicago 10, Illinois.

All inquiries pertaining to the meeting should be addressed to the chairman of the International and Fourth American Congress on Obstetrics and Gynecology, Dr. Fred L. Adair, at 24 West Ohio Street, Chicago 10, Illinois. Mr. Karl S. Richardson is business manager.

SOCIETY MEETINGS AND CONFERENCES

JANUARY 7-APRIL 13 American College of Surgeons. Sectional Meetings. Page xi. Issue of December 23.

FEBRUARY 14 New England Heart Association. Page 160. Issue of January 27.

FEBRUARY 15 South End Medical Club. Page 239.

FEBRUARY 15 Greater Boston Medical Society. Page xvii. Issue of February 3.

FEBRUARY 23 Norfolk District Medical Society. Notice above.

FEBRUARY 25 Boston Surgical Society. Notice above.

FEBRUARY 28 Norfolk District Women's Auxiliary. Notice above.

MARCH 7-9 American Academy of General Practice. Page 728. Issue of November 4.

MARCH 10 Evaluation of the Treatments of Arthritis. Dr. Walter Bauer. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

MARCH 28-APRIL 1 American College of Physicians. Page 138. Issue of July 22.

APRIL 5-8 Postgraduate Institute of Philadelphia County Medical Society. Notice above.

MAY 4 New England Obstetrical and Gynecological Society. Springfield Country Club. Springfield.

MAY 16-19 American Urological Association. Biltmore Hotel. Los Angeles, California.

MAY 24-26 Massachusetts Medical Society. Annual Meeting. Worcester Memorial Auditorium. Worcester.

MAY 26-28 American Gynecological Association. Hotel Lorraine. Madison, Wisconsin.

MAY 30-JUNE 3 International Congress on Rheumatic Diseases. Page 800. Issue of November 18.

JUNE 20-23 Annual Conference of Health Officers and Public Health Nurses. Page xvii. Issue of February 3.

SEPTEMBER 28-30 Mississippi Valley Medical Society. Page 1050. Issue of December 30.

NOVEMBER 2 New England Obstetrical and Gynecological Society. Hotel Somerset. Boston.

NOVEMBER 11-17 Third Inter American Congress of Radiology. Page 158. Issue of July 22.

MAY 14-19 1950 International and Fourth American Congress on Obstetrics and Gynecology. Notice above.

(Notices concluded on page xvii)

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AUREOMYCIN IN THE TREATMENT OF PRIMARY ATYPICAL PNEUMONIA*

MAXWELL FINLAND, M D,† HARVEY SHIELDS COLLINS, M D,‡ AND EDWARD BUIST WELLS, M D§

BOSTON

THE disease generally known as "primary atypical pneumonia" or "viral pneumonia" is now well established as a clinical entity. The fully developed case can usually be recognized by the nature and course of the symptoms, the character of the physical and roentgenographic findings in the lungs, the absence of sustained leukocytosis and the failure to find significant pathogenic bacteria in the blood, sputum or lungs or to obtain clinical cures with the available antibacterial agents. Confirmation of the diagnosis is obtained in a large proportion of cases by the demonstration of cold agglutinins in the patients' blood late in the acute disease or during convalescence.

The ambiguous status of the etiology of this disease is still well characterized by the designation recommended early in the war by the Army Epidemiological Board, namely, "primary atypical pneumonia, etiology unknown."¹ The viral nature of the etiologic agent is strongly suggested by the transmissibility of the disease to normal human subjects by means of bacteriologically sterile filtrates of sputum from active cases.² The only viral agent transmissible to laboratory animals that seems to fulfill the criteria for the etiology of this disease is that of Eaton,³ but his findings still await confirmation by other workers. Furthermore, the finding of certain strains of nonhemolytic streptococci in cultures of lungs and sputum of a number of cases of this disease and the demonstration of agglutinins for these streptococci during convalescence in a significant proportion of cases suggest a possible synergism of such bacteria and some unknown virus in the causation of the disease.⁴ There is also the possibility and even likelihood that several distinct nonbacterial agents, as yet undiscovered, produce the same clinical picture.

Irrespective of its etiology, it is generally agreed that there is no definitive therapy for this disease entity. All workers agree that the sulfonamides and penicillin are entirely ineffective in primary atypical pneumonia except possibly so far as they may influence bacterial complications, and even the evidence for the occurrence of such complications in any appreciable number of cases is quite meager. Although streptomycin is also usually included among the antibacterial agents that are said to be without effect on this disease, published reports of its use under controlled conditions in any significant number of cases could not be found.⁵ Convalescent serum does not offer a practical therapeutic approach, and even the favorable reports of its use are not entirely convincing.

The discovery of aureomycin,⁶ an antibiotic agent that is highly effective against infections with all the known rickettsias and the viruses of the psittacosis-lymphogranuloma-venereum group in animals and in such human cases as there has been opportunity to observe to date, is of particular interest in relation to primary atypical pneumonia. The manifestations of human infections with psittacosis and Q fever are virtually indistinguishable from those of primary atypical pneumonia in which the etiologic role of these or any other known agents can be ruled out. Moreover, other rickettsias, such as those causing epidemic typhus, which are not usually thought of as causes of pneumonia, may produce symptoms and pulmonary lesions that are indistinguishable from those of primary atypical pneumonia except by specific serologic tests or by isolation of the rickettsia. It seems quite possible, therefore, that some as yet undiscovered agent or agents of one of these groups cause some of the cases now classified as primary atypical pneumonia, etiology unknown.

At any rate, it seemed quite reasonable to attempt empirically to determine whether aureomycin would favorably influence the course of this disease. Furthermore, the wide "valence" of the activity

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School. Aided by a grant from the U. S. Public Health Service.

†Associate professor of medicine, Harvard Medical School, chief, Fourth Medical Service, and associate physician, Thorndike Memorial Laboratory, Boston City Hospital.

‡Milton Fellow, Harvard Medical School, research fellow, Thorndike Memorial Laboratory, Boston City Hospital.

§Research fellow in virus diseases, National Research Council, research fellow, Thorndike Memorial Laboratory, Boston City Hospital.

⁵In a cursory review of the literature dealing with either streptomycin or primary atypical pneumonia, direct reference was found to only 2 cases and in both of them the streptomycin had no effect on the course of the disease.

of aureomycin and its relatively low toxicity served to minimize the hazards of a clinical trial with this agent, since it has been found to be effective both in vitro and in vivo against a large variety of gram-positive and gram-negative bacteria, including those that are commonly found as causes of pneumonia.⁶ A preliminary clinical trial in a few cases of pneumococcal pneumonia yielded results comparable with those obtained in similar cases treated with sulfadiazine or penicillin.⁷

It is the purpose of this paper to present and discuss some observations made in the course of the clinical evaluation of the effects of aureomycin

consider for aureomycin treatment only cases of at least moderate severity in which the clinical and x-ray picture was clearly defined and the patient was acutely ill at the time. When the patient was first seen, the duration of symptoms of the disease was estimated as nearly as possible. This was not always a simple matter because of the occurrence of upper respiratory symptoms before or during the illness and the relation of these symptoms to the pulmonary infection could not be readily assessed. When there was any reason to suspect that the acute disease was receding, as evidenced by recent improvement in the general appearance of

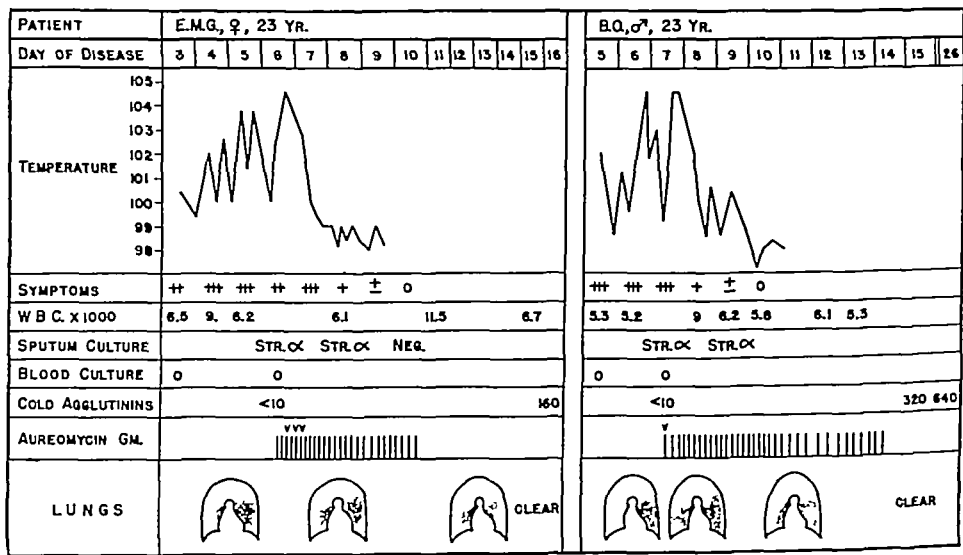


FIGURE 1 Primary Atypical Pneumonia Treated with Aureomycin by Mouth

in a few selected cases of primary atypical pneumonia. The cases are presented from the point of view of the critical interpretation of these observations rather than in any attempt to arrive at a definitive conclusion concerning the actual effectiveness of aureomycin in this disease. The latter must await experiences with a considerably larger number of cases.

MATERIALS AND METHODS

Selection of Cases

The patients included here were all young adults either from the various medical services of the Boston City Hospital or from other nearby hospitals where they were observed and the data obtained through the courtesy of their attending physicians.

On the assumption that the great majority of cases of primary atypical pneumonia are quite mild and offer considerable difficulty in interpretation of the effects of the trial agents, it was decided to

the patient or in the fever or symptoms, the patient was first observed for a few hours. The aureomycin was then given only if the temperature rose again and the symptoms returned to the previous severity or got worse, and the antibiotic was withheld if the improvement continued. If other drugs or antibiotics had been used, this delay afforded additional time for evaluation of their effects.

Laboratory Studies

The usual laboratory data, including blood and sputum cultures and white-cell counts, were obtained. In addition, blood was taken for estimation of the cold-agglutinin titers and for other serologic tests before treatment was started and again at suitable intervals.

Dosage

All the aureomycin was given by mouth in the form of capsules of the crystalline hydrochloride. The dosage used was 1 gm. every four to six hours until the temperature had become essentially nor-

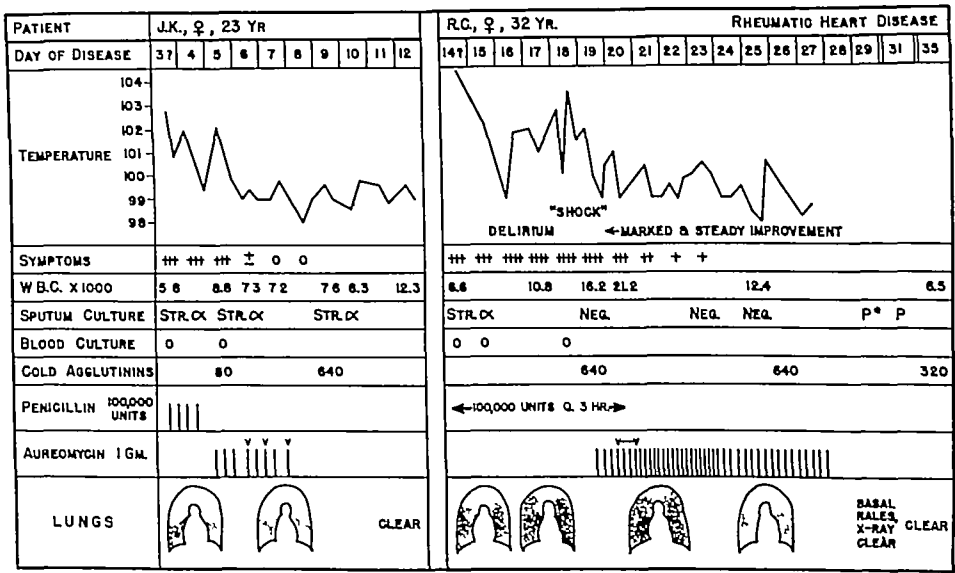
mal for a few hours and every six to eight hours for an additional two or three days. The less frequent doses were usually employed in patients who exhibited nausea or vomiting. This dosage was chosen arbitrarily and no attempt has been made, as yet, to determine the optimum dose.

CLINICAL RESULTS

All the patients included in this study had the classic clinical and laboratory findings of primary atypical pneumonia. The onset was rather insidious, with chills or chilly sensations, and these were followed by increasing malaise, rather severe

tive, and cultures of the sputum yielded only the common mouth organisms, *Streptococcus viridans* usually predominating. Significantly high cold-agglutinin titers, usually 1:160 or higher, were attained in the serum at the proper time in every case.

The number of patients who have been treated with aureomycin to date is too small for any statistical evaluation. In every case, however, the temperature fell to and stayed at normal levels within twelve to thirty-six hours of the first dose, and this was accompanied by a loss in "toxicity" and improvement in the systemic and respiratory symp-



*P=OVERGROWN BY PROTEUS.

FIGURE 2 Primary Atypical Pneumonia Treated with Aureomycin by Mouth

generalized headache, prostration, irritating cough, which was either dry or productive of scanty yellowish mucoid sputum, and soreness of the anterior portion of the chest and costal margins but no true pleuritic pain. In most cases there was only slight if any dyspnea or cyanosis when the patient was at rest, but these symptoms were present or became accentuated on very slight exertion. There was only slight or moderate dullness to percussion over some parts of the lungs, with only minor or transient changes in the breath sounds or the whispered and spoken voice, but in every case there were large areas of the chest over which showers of medium crepitant rales were heard. Roentgenograms showed the characteristic soft nodular shadows scattered through extensive areas of the lungs, and some also showed patchy areas of partial atelectasis. The white-cell counts were essentially normal except for slight and transient leukocytosis in some cases. Blood cultures were all nega-

toms, without further demonstrable extension of the pulmonary lesions and with evidence of progressive clearing of the lungs thereafter. Nausea — with or without vomiting, which seemed to occur quite frequently with some of the lots of aureomycin given in large doses — seemed to obscure the early symptomatic improvement in some of the patients, but this usually subsided as recovery set in even though the administration of the antibiotic was continued. The findings are best illustrated by a brief résumé of the first 4 cases in which the aureomycin was used. Some of the more relevant data in these cases are shown in Figures 1 and 2.

E. M. G. (Fig. 1) was first considered for aureomycin therapy on the 6th day of illness. There had been downward swings in the temperature on that day and on previous days, but each of these had occurred in response to the administration of aspirin and each was followed by rises to or above the previous peaks with aggravation of the headache and systemic symptoms. Aureomycin was started during an upward swing in fever and no further aspirin was given. The temperature reached normal and

of aureomycin and its relatively low toxicity served to minimize the hazards of a clinical trial with this agent, since it has been found to be effective both in vitro and in vivo against a large variety of gram-positive and gram-negative bacteria, including those that are commonly found as causes of pneumonia.⁶ A preliminary clinical trial in a few cases of pneumococcal pneumonia yielded results comparable with those obtained in similar cases treated with sulfadiazine or penicillin.⁷

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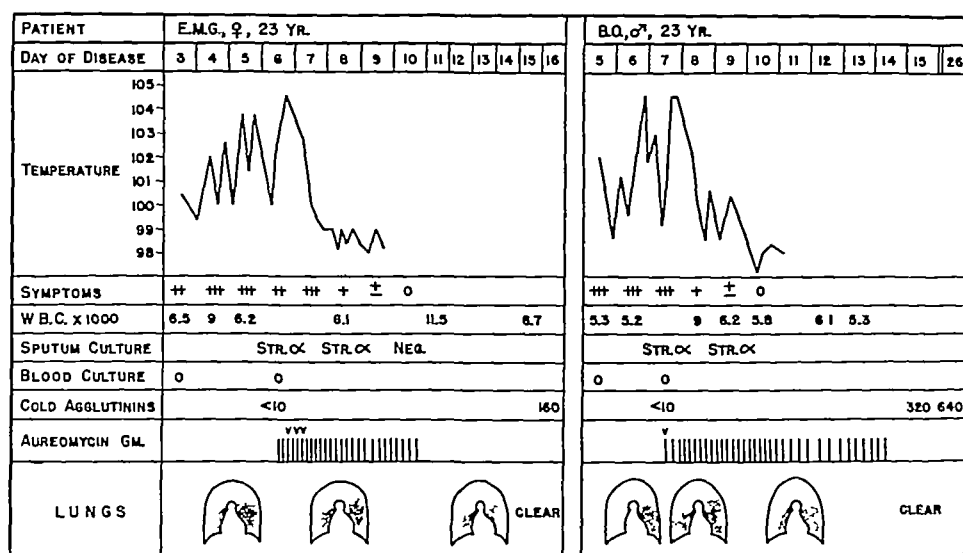


FIGURE 1 Primary Atypical Pneumonia Treated with Aureomycin by Mouth

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On the assumption that the great majority of cases of primary atypical pneumonia are quite mild and offer considerable difficulty in interpretation of the effects of the trial agents, it was decided to

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Laboratory Studies

The usual laboratory data, including blood and sputum cultures and white-cell counts, were obtained. In addition, blood was taken for estimation of the cold-agglutinin titers and for other serologic tests before treatment was started and again at suitable intervals.

Dosage

All the aureomycin was given by mouth in the form of capsules of the crystalline hydrochloride. The dosage used was 1 gm. every four to six hours until the temperature had become essentially nor-

then started on injections of 0.5 gm of streptomycin every 6 hours and when first seen she had already received four such injections. During the 4 hours immediately preceding this visit the temperature had dropped appreciably, she was free of headache, and the malaise had eased considerably for the first time without antipyretics or analgesics. The streptomycin was continued for another 36 hours, during which she became entirely afebrile and symptom free and the lungs began to clear rapidly. Further injections of aqueous penicillin were given by a physician "to prevent secondary bacterial infection" while she remained in the hospital.

S S had a more severe illness and more extensive pulmonary involvement when he was first seen by one of us at a hospital in another city. It was the 9th day of illness, and he had received moderately large doses of penicillin during the previous week and these doses had been increased on that day. In addition, at the end of the 7th day, when the temperature reached 104.8°F, the pulmonary lesion had spread and the patient appeared to be getting much

mild or seemed to be improving either without specific therapy or while only penicillin was being given. The course of events in a patient in whom penicillin therapy was continued without the addition of either streptomycin or aureomycin may be mentioned. This patient was seen with a view to aureomycin therapy during the low points of his fever on the fourth and fifth days of his illness. On each occasion antipyretics had not been given, and it was believed that the patient might be improving spontaneously so that if aureomycin were started at that time it would not be possible to assess its effects. The course of this patient during the next ten days was characterized by a low-grade fever, severe cough, moderate malaise and head-

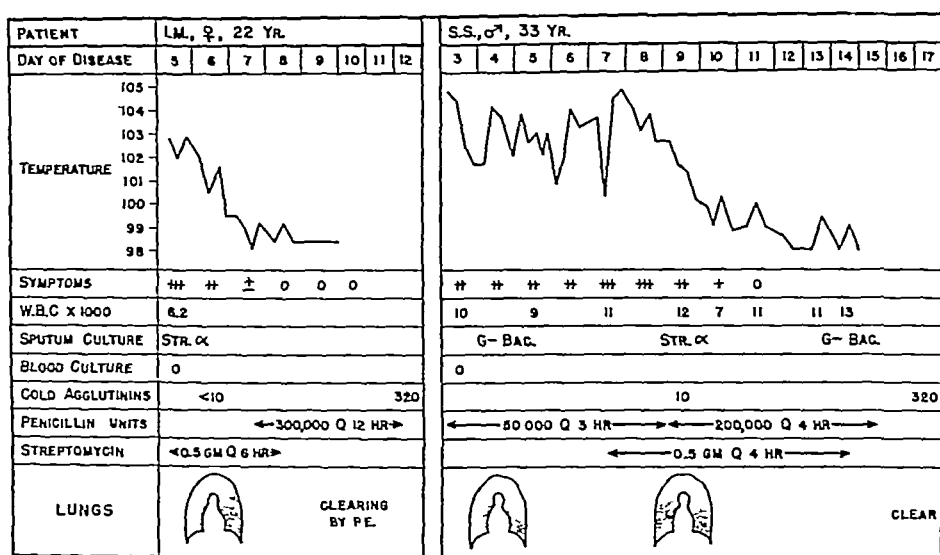


FIGURE 3 Primary Atypical Pneumonia Treated with Penicillin and Streptomycin

worse, he was started on injections of streptomycin (0.5 gm every 4 hours). He had already received a total of 5 gm at the time when he was seen. It was then apparent from his temperature chart that his fever was receding gradually but steadily, and, although he was still moderately ill, slightly cyanotic and sweating profusely, he readily admitted that he had been improving steadily in every respect during the preceding day. Aureomycin was, therefore, withheld, and, under further observation, he continued to improve steadily and his lungs began to show signs of clearing during the next 2 or 3 days.

The acute febrile illness terminated on the seventh day in I M and on the tenth or eleventh day in S S. In both patients, as in the 2 cases shown in Figure 1, there were no cold agglutinins in the serum when aureomycin therapy was first considered, and high titers appeared in later specimens in each case. The effect of streptomycin in these 2 patients obviously cannot be assessed with certainty, but the favorable course following its use at least suggests that this antibiotic had a beneficial effect on the course of their disease.

In an occasional patient the symptoms during the first day or two of observation were relatively

ache, with some extension of the pulmonary lesion by physical and x-ray examination. Cold agglutinins, which were absent at first, were present in low titer on the eleventh day and in a much higher titer a week later. This case illustrates the fact that it has not been possible, on the basis of observations made during the first few days of the acute illness, to predict the subsequent course of the disease.

The question then is, How may one arrive at a reasonable estimate of the true value of these apparently effective agents in a disease with so variable a course as primary atypical pneumonia in which the early stages are so ill defined? It seems obvious from the cases presented that if treatment with the trial agents is withheld until the patients show progressively increasing severity of the symptoms or extension of the pulmonary lesions, the use of these agents will be confined essentially to a stage of the disease when the illness may be expected to terminate spontaneously in increasing proportions of cases.

remained so within 18 hours. Symptomatically, the patient complained of marked nausea, and she vomited three of the doses during the first 24 hours. She improved steadily thereafter, and the nausea and vomiting subsided in spite of the fact that aureomycin was continued for 3 more days. The lungs began to clear promptly and were entirely clear by physical and x-ray examination a week after the antibiotic had been started.

The course of events in B O (Fig 1) was quite similar. Some of the downward swings in temperature followed the taking of aspirin, and others followed alcohol sponge baths. Aureomycin was first given on the 7th day of illness when the temperature was again rising and the lesion in the lung was apparently spreading. This patient vomited once after the first dose, but the temperature dropped precipitately and he was markedly improved within 24 hours of the first dose. The signs in the lungs began to clear in the next 2 days and were entirely clear within 1 week.

Neither of these patients received any other antibiotics or any sulfonamide therapy. Both were essentially well by the eighth or ninth day of the disease. Inasmuch as spontaneous improvement at that time occurs quite frequently in this disease, it cannot be stated with any assurance that the termination of the acute illness in these patients was caused by the aureomycin in spite of the fact that the course of the symptoms in relation to the administration of the antibiotic is strongly suggestive. The absence of cold agglutinins at the time treatment was started and their presence in high titer later may be taken as additional evidence favoring such an interpretation.

In J K (Fig 2) it was difficult to determine the exact duration of the pneumonia. This patient had had an upper respiratory infection with coryza, headache, mild fever and slight nonproductive cough for 2 weeks before she came to the hospital. During this time she had slight chilly sensations and sweats, but she had been taking aspirin frequently and was able to stay at her work until 2 days prior to admission. At that time she had a shaking chill, followed by a severe headache and exacerbation of the previous symptoms with more frequent and severe paroxysmal cough productive of greenish and occasionally blood-tinged sputum. She was given sulfadiazine by a physician, but the symptoms grew steadily worse. She became nauseated and vomited. She was then referred to the hospital, where she remained acutely ill for 2 more days under penicillin therapy. On the 3rd hospital day, when the temperature was again rising, she was started on aureomycin. The fever and symptoms began to improve promptly and she was afebrile and her systemic symptoms had largely subsided in less than 24 hours after the first dose. This patient had some nausea, and she vomited three of the doses on the 2nd and 3rd days and the drug was then discontinued. The lungs began to clear at this time and were entirely clear by physical and x-ray examination 1 week later.

In this case, again, the prompt improvement that followed the administration of aureomycin strongly suggested a causal relation. The finding of an elevated cold-agglutinin titer when this treatment was started, even though the titer later rose significantly, suggests that the disease was of two weeks' rather than five days' duration at that time. The possibility of a normal termination of the acute illness coincidental with the start of aureomycin therapy must, therefore, be considered.

The course of events in R C (Fig 2) again strongly suggests a remarkable and prompt effect from aureomycin, but a critical evaluation of all the data likewise raises con-

siderable doubt. This patient, who was known to have had rheumatic heart disease for at least 7 years, had been ill at home for 2 weeks with chills and fever and a hacking cough productive of yellow and occasionally "frothy, pink" sputum. During this time she was treated with sulfadiazine, but she became much worse 2 or 3 days prior to entry, when she was thought to have cardiac failure and so was sent to the hospital. The symptoms and signs in the lungs at the time of admission were consistent with either diffuse pulmonary congestion or extensive pneumonia, or both. She failed to respond to cardiac therapy and to large doses of penicillin and became confused and disoriented, dyspneic and cyanotic and finally appeared to be in "shock." On the 6th hospital day while in this condition she was started on aureomycin. All the symptoms showed perceptible improvement 18 hours after this therapy had been started and within the next 2 days she was remarkably improved so that her appetite returned and she breathed much more comfortably. The lungs began to clear rapidly, and she was free of all symptoms by the end of the 1st week. Except for a few basal rales the lungs were entirely clear after 2 weeks.

In this patient a high titer of cold agglutinins at the time aureomycin was started was consistent with the long duration of the illness at that time. Although this suggests that the recovery was spontaneous, all the physicians who observed the patient were convinced that she was failing rapidly, that her chances of recovery were very slight indeed when treatment with aureomycin was started and that the administration of this agent was in large measure responsible for the beginning of her recovery.

In the other patients with primary atypical pneumonia who were treated with aureomycin the course before and after this treatment was essentially similar to that noted in the cases cited above. There was also similar difficulty in assessing the role of the aureomycin in each patient, in spite of the fact that they were all acutely ill and not showing evidence of improvement when administration of this antibiotic was started.

During the period when these cases were being observed, however, a considerably larger number of patients with similar clinical findings were seen but in them aureomycin treatment was withheld. These patients differed from the first group only in that, either subjectively or objectively, they seemed to be improving sufficiently to suggest that they were approaching the termination of their acute illness although they were still febrile and moderately ill when they were first considered for aureomycin therapy. In almost every case the subsequent clinical course was in every way similar to that of the 3 cases cited above, in spite of the fact that aureomycin was not used. Two of these cases are of particular interest because the findings suggest that clinical improvement occurred in response to the administration of streptomycin. Some of the relevant findings in these 2 cases are shown in Figure 3.

I M was first seen with a view to aureomycin therapy on the day after admission to another hospital. It was the 6th day of illness, and the symptoms were becoming progressively worse. She had received injections of 300,000 units of procaine penicillin in oil on each of the 2 days preceding admission, and this had been discontinued. She was

OVARIAN NEOPLASMS IN A HERMAPHRODITE*

THOMAS F. CORRIDEN, M.D.†

NORTHAMPTON, MASSACHUSETTS

HERMAPHRODITISM in itself is a rare anomaly. The additional occurrence of bilateral gonadal neoplasms is exceedingly uncommon. The present paper reports the case of a "male" hermaphrodite with a pseudomucinous cystadenoma of the right ovary and a dysgerminoma (seminoma) of the opposite gonad.

GENERAL CONSIDERATIONS

Hermaphroditism is the term used to designate the congenital possession by one person of both male and female sex organs. Two forms exist, true hermaphroditism and pseudohermaphroditism. Diagnosis of the former requires the presence of both ovary and testis either as separate organs or combined to form unilateral or bilateral ovotestes. In pseudohermaphroditism, on the other hand, the gonads are either ovarian or testicular, and only the secondary sex organs are both male and female.

True hermaphroditism is quite rare, only 38 cases appearing in the literature.¹ Pseudohermaphroditism, in contrast, is stated to occur to some degree in 1 out of every 1000 females, it is considerably less frequent in males.¹

Tumors occurring in hermaphrodites may arise from ovarian or testicular tissue, in pure organs or in ovotestes, often the gonad is destroyed by the neoplastic process so that the site of origin is impossible to determine.

No neoplasm is found in constant association with hermaphroditism. The most commonly reported one is the dysgerminoma,² a highly radiosensitive malignant tumor composed of large, clear epithelial cells growing in diffuse sheets or nests isolated by a stroma rich in lymphocytes. According to Meyer³ the dysgerminoma is a tumor of the neuter germ cell of the embryo, it arises in ovarian or testicular tissue, in the latter site it is better known by the names, seminoma⁴ and embryonal carcinoma.⁵ Meyer³ collected 27 cases of dysgerminoma occurring in hermaphrodites. Five were bilateral. Two of the 27 patients had an ovotestis on the side opposite the tumor.

In addition to hermaphrodites the dysgerminoma tends to occur in persons with less striking sexual abnormalities, including male cryptorchidism and female hypoplasia of the genital organs. The majority of dysgerminomas, however, arise in apparently normal men and women.⁶

Beyond the observation that dysgerminomas are encountered with unusual frequency in persons who

approach neutrality in sex, there is no apparent causal relation between dysgerminoma and hermaphroditism, for the latter is a congenital malformation that remains despite removal of the tumor.

A second tumor that has been reported with some frequency in hermaphrodites is the so-called tubular adenoma of the testis.⁷ This occurs as single or multiple small nodules in the cryptorchid testicles of both normal and hermaphroditic patients. It appears in most if not all cases to be a nodular hyperplasia in an atrophic, cirrhotic organ rather than a true neoplasm, it has no clinical significance.

One of the most controversial aspects of hermaphroditism is the proper classification of patients with arrhenoblastomas — that is, ovarian neoplasms that resemble testicular tissue and often cause masculinization. These tumors range from tubular adenomas, which may bear a striking resemblance to the so-called adenomas of the cryptorchid testicle, to highly undifferentiated sarcomatoid forms. According to Pick,⁸ the tubular adenoma arises in the testicular portion of an ovotestis, hence, a person with such a tumor is a hermaphrodite by definition. Meyer,³ on the other hand, believed that the assumption of the existence of an ovotestis is not necessary since the embryonic rests of testicular tissue present in the normal ovary adequately account for the occasional occurrence of masculine tumors. In support of this is the fact that convincing evidence of congenital hermaphroditism is quite rare in patients with tubular adenomas.⁹

Gonadal neoplasms other than dysgerminoma and testicular adenoma have been reported in small numbers of hermaphrodites.^{9, 10} No case of pseudomucinous cystadenoma of the ovary was encountered in an extensive, albeit incomplete, review of the literature.

CASE REPORT

A 38-year-old patient, stated to be a man, who was married but had no children, was admitted to the hospital complaining of pain and discomfort in the abdomen.

The father was living, aged 77. The mother had died in 1927 from leukemia. One sister was living and well, she was married and had 3 children.

At the age of 1½ the patient was in the hospital for some sort of operation on the penis, and at the age of 3 he was confined to the hospital because of trouble with urination. From that time until he was 35 he had absolutely no trouble.

For a year prior to admission to the hospital the patient had been having episodes of pain and discomfort in the abdomen associated with nausea and vomiting. He had been married for 11 years and as far as could be ascertained he had sexual relations with his wife. Four weeks before admission the patient had suffered low-back pain and diarrhea. There were no bloody stools. The pain gradually migrated laterally to the mid-lower abdomen.

The temperature was 99.5°F by rectum. The blood pressure was 150/70, the pulse 85 and the respirations 20.

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†Chief Surgical Service, Cooley Dickinson Hospital, consultant, Northampton State Hospital.

Were all cases to be treated as soon as the diagnosis of primary atypical pneumonia is made or suspected on clinical grounds, the great majority of the patients treated might turn out to have either a disease that is ill defined (undifferentiated acute respiratory disease⁸) or at most a rather mild case of primary atypical pneumonia in which the effects of the agents would be difficult to assess. Proof of the effectiveness of these agents in the cases that proved to be primary atypical pneumonia would, in any event, have to depend on the demonstration of a constant beneficial effect in consecutive cases and in direct relation to the initiation of the treatment. In addition, adequate causes, extraneous to the primary pulmonary infection, would have to be established to account for the failures.

On the other hand, should any appreciable number of such patients show a progression of symptoms and pulmonary lesions under adequate doses of one of these agents, it would be possible to state with some assurance that that agent was not specifically effective in this disease. On the basis of this argument, the few cases of primary atypical pneumonia in which streptomycin is said to have had no effect on the course of the disease are more significant than the 2 cases in which a possible beneficial effect was noted, provided, of course, that the same criteria were used for diagnosis.

The patients with whom we are concerned in the present evaluation were acutely ill and febrile when aureomycin was started, and each had a history and physical examination. X-ray and laboratory findings were characteristic of primary atypical pneumonia. The first 20 consecutive patients who satisfied these criteria and, in addition, developed significant titers of cold agglutinins in their blood at the appropriate time were all markedly improved clinically and were afebrile within twelve to forty-eight hours (the great majority within twenty-four hours) after the first dose of aureomycin was given. The pulmonary lesions then cleared rapidly in every case. On the basis of these consecutive favorable responses, therefore, aureomycin may be said to be highly effective in the treatment of cases of primary atypical pneumonia of the variety that is associated with the development of cold agglutinins. Further details of these cases and the findings in cases of other types of pneumonia that have been treated with aureomycin will be given in a later report.

While this study was in progress, similar studies on the effects of aureomycin in primary atypical

pneumonia were being carried out by several other groups of workers. Reports from two of these groups, one from New York⁹ and the other from Baltimore,¹⁰ have already appeared. In each instance favorable responses similar to those reported here were noted in consecutive cases of this disease, and in the majority of the cases cold agglutinins were demonstrated at the appropriate time. Both groups of workers are convinced that aureomycin has a definitely favorable effect on this disease.

SUMMARY

A small group of patients with the characteristic clinical, x-ray and laboratory findings of primary atypical pneumonia were treated with aureomycin by mouth. They were all moderately or severely ill when this treatment was started, and their fever and symptoms began to improve promptly and subsided in all cases within twelve to forty-eight hours. Cold agglutinins appeared in high titer late in the acute illness or during convalescence in the serum of all of these patients. The findings in these cases suggest that aureomycin had a favorable effect on the course of the disease.

Two cases are presented in which a somewhat similar course of events followed the administration of streptomycin.

The problem of the evaluation of curative agents in primary atypical pneumonia is discussed in relation to the findings in these cases.

We are indebted to Mildred W. Barnes for carrying out the cold-agglutination tests, and to Clare Wilcox for bacteriologic studies of the sputums.

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RIGHT- OR LEFT-HANDEDNESS*

A Practical Problem

RICHARD S. EUSTIS, M.D.†

CHESHAM, NEW HAMPSHIRE

A PHYSICIAN who is asked if it is safe and wise to train an apparently left-handed child to use pencil and pen with his right hand can find good authority in the literature for almost any answer he may choose to give. The more he studies the subject, the more confusing it becomes. The theories propounded are various and conflicting.

If he then tries to form his own opinion by testing and observing his patients he soon finds that his decision whether a given child is right-handed, left-handed or ambidextrous often depends on the number and type of tests used. If his bias is toward a comparatively large number of ambidextrous subjects, all he need do is administer a large battery of laterality tests that include the relatively unskilled activities. On the other hand, a smaller battery testing chiefly the skilled activities will give less evidence of ambidexterity and more of definite right-handedness or left-handedness. There are many exceptions, but by and large the more tests that are given and the more the untrained activities are included the greater the amount of mixed or confused dominance that will be found.

The problem of handedness is actually a double one, although the duality is ignored by many. The first question is why man alone among primates has developed a preferred hand, and the second is why in approximately 95 per cent of adult, civilized, tool-using peoples the preferred hand is the right.

GENERAL CONSIDERATIONS

Although man from most anatomic points of view is a bilaterally symmetrical animal, he is in reality decidedly asymmetrical in function. Attempts have been made to demonstrate this asymmetry in some of the lower animals, such as the rat, horse, dog, monkey and ape. It cannot be denied that some of these at times show a preference for one side over the other, but this vague, indefinite preference is far from the skilled, unilateral handed-

ness shown by the great majority of human adults. Monkeys and apes have developed unilaterality a little farther than the others in that they manipulate an object with one hand while the other is used for support or for holding and steadying, but they seem to have no great preference regarding the hand that does the manipulating. The ability to develop a preferred and hence more skillful hand is a characteristically human trait, which apparently has arisen as an inevitable result of man's one-handed use of tools and weapons. It seems clear that the acquisition of skill in one hand is a gradual process largely dependent upon training through habitual use.

Man's unilateral handedness, however, is fluid, not fixed. What one hand can do the other can also do, although until practiced it is slow, clumsy and awkward. This bimanual ability is exemplified by the skill of the pianist and typist with the ordinarily nonpreferred hand. The fluidity is particularly marked in childhood when the preferred hand is still far from skillful and the nonpreferred hand can do almost as well as the other.

HANDEDNESS IN INFANCY

Handedness in infancy means only the somewhat more frequent use of a particular hand for reaching, touching and eventually grasping objects. This sort of activity is very different from the handedness of an adult, whose habitual use of one hand has greatly increased its skill. In the infant and young child the more frequently used hand shifts from side to side at fairly definite intervals, with periods when both hands are used either together or with no choice between them.¹⁻⁵ The studies of Conel⁶ suggest that this alternation in use depends upon changes and new connections in the constantly growing association tracts. Whatever the cause may be, the practical result is that both hands receive some training, so that the final outcome is, "not a good hand and a poor one, but a good hand and a better one."

*From the Language Clinic, Massachusetts General Hospital.

†Member, Board of Consultation, Massachusetts General Hospital.

Physical examination revealed a rather short, stocky, slightly obese man weighing about 140 pounds. The patient had a normal beard and a normal distribution of hair over the entire chest. Examination of the abdomen revealed a slight bulge in the right lower quadrant. Palpation disclosed a smooth, round, nontender tumor. The left side of the lower abdomen appeared normal. Examination of the genitalia showed a normal growth of pubic hair, with complete absence of the scrotum. There was a typical hypospadiac penis, which was small (approximately 4 cm long). The prepuce was not covered with skin. Approximately 4 cm back from the head of the prepuce there was an opening through which he urinated. There was no opening in the head of the penis. Rectal examination was entirely negative.

A barium enema showed the colon to fill and evacuate well, without evidence of intrinsic disease. A normal-appearing appendix was visualized. There was a discretely outlined oval mass, 11 by 15 cm, displacing the cecum upward. The mass was situated in the right lower hypogastrium and pelvis. The impression was that of a malignant tumor, as noted, originating in an undescended testis. Pyelography was recommended to rule out the lesser possibility of renal tumor.

Intravenous pyelography showed normally draining structures bilaterally. The only abnormality to be seen was a slight extrinsic pressure defect on the right ureter, displacing it medially.

The diagnosis was abdominal tumor, probably testicular in nature. Under continuous spinal anesthesia a long incision was made in the right lower quadrant. When the abdomen was opened a large, round, smooth, thin-walled tumor, apparently ovarian in origin, was found. The tumor, approximately 15 cm in width, was attached to a small, hard mass, which was posterior to the urinary bladder. Further observation disclosed a large, hard, irregular mass, measuring 8.5 by 7 by 3 cm, in the left pelvis, which was well encapsulated and firm to palpation. The incision was enlarged, and further examination revealed a small, hard, fairly well developed uterus, which ran off into a small tubular structure just beneath the bladder. At this time a sound was passed through the meatus and could be palpated in the urinary bladder. The small tubular structure evidently ended in the peritoneum of the pelvic wall. Both tumors with the tissue attached to them were removed and given to the pathologist. Nothing further was done. The abdomen was closed without incident.

Postoperatively the patient did extremely well except for the 2nd night after operation, when he began to complain of severe hot flashes. He was given stilbestrol, 0.1 mg nightly. After a few days the hot flashes diminished. He was discharged from the hospital 12 days after the operation and has since been on stilbestrol therapy.

The pathological report was as follows:

The gross specimen consists of a cyst (from the right pelvic mass) measuring 15 by 13 by 8.5 cm. It is translucent, and when the wall is incised, it is found to contain about 750 cc of a clear, serous fluid and the cyst is multiloculated. The inner lining of the cyst is smooth. One of the cysts is filled with a chocolate-colored material.

There is an irregular, lobulated mass (from the left side of the pelvis) measuring 8.5 by 7 by 3 cm. It appears well encapsulated and is fairly firm to palpation. On section it is almost solid and is yellow gray. The cut surface is glistening. Attached to one side of this tumor is a tubular structure, which grossly resembles a fallopian tube.

Two sections taken from the cyst of the right gonad show a multilocular, pseudomucinous cystadenoma. The cysts, which vary considerably in size, are surrounded by dense collagenous tissue that bears a striking resemblance to ovarian stroma. The cyst lining varies from a columnar mucus-secreting epithelium to an indifferent squamous one, in some areas the lining cells are piled up, however, there is no evidence of malignancy. Occasional cysts are filled with serous fluid. The stroma surrounding the cysts may be extremely cellular with crowded, plump fibroblasts or may show hyalinization. In the cellular areas cords of epithelioid cells become intimately mixed with the stromal elements. The former are polyhedral and are characterized by distinct cell borders, abundant pale cytoplasm denser centrally, and pale, round, central nuclei, their appearance is suggestive of theca interna cells. The tumor is encapsulated by a layer of dense collagenous tissue resembling

tunica albuginea. No testicular or specific ovarian elements (other than stroma) can be identified in the sections. External to the capsule of the tumor is a tubular structure that has the characteristics of the isthmus portion of a fallopian tube.

One section taken from the tumor of the left gonad shows a dysgerminoma characterized by interlacing cords and alveoli of uniform polyhedral cells separated by a collagenous stroma rich in lymphocytes. The cytoplasm of the tumor cells is clear and has a somewhat vacuolated appearance owing to post-mortem degeneration. The nuclei are round to oval, contain heavy granular chromatin and show slight to moderate variation in size and shape. There are occasional mitoses. Small numbers of epithelioid cells and multinucleated giant cells filled with fine fat droplets are present, especially at the periphery of the cords. The tumor is encapsulated by a layer of dense collagenous tissue resembling tunica albuginea. No testicular or ovarian tissue is identifiable.

A final section taken from the tubular structure attached to the left gonadal tumor shows epididymis and a large duct lined by alternating groups of tall and low cells, giving the lumen a festooned circumference, which suggests that the duct is a ductulus efferens of the testis despite its large size.

The diagnoses are dysgerminoma of the left ovary, pseudomucinous cystoma of the right ovary and rudimentary fallopian tube.

DISCUSSION

In summary, this patient had both male and female secondary sexual organs. Was "he" a true hermaphrodite or a female pseudohermaphrodite? There is considerable evidence that the right gonad was an ovary; it was occupied by a pseudomucinous cystadenoma in which the cysts were surrounded by typical ovarian stroma*, pseudomucinous cystadenomas do not, to my knowledge, arise in the male gonad, and there was clinical evidence of estrogen withdrawal postoperatively. It is entirely possible that the cords of epithelioid cells in the stroma were estrogen-producing theca interna cells or that the stroma itself was estrogenic.

The identity of the left gonad presents an insoluble problem, no traces of testicular or ovarian tissue were present in the section of tumor. The tumor itself was consistent with an origin in either testis or ovary. The degree of nuclear hyperchromatism of the neoplastic cells is, in my opinion, a more common feature of the ovarian rather than the testicular dysgerminoma, this evidence, however, is only suggestive. In conclusion, then, it is believed that there is somewhat more evidence that this patient possessed two ovaries, and hence was a female pseudohermaphrodite. This conclusion is given some statistical support by the great rarity of true hermaphroditism.

16 Center Street

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RIGHT- OR LEFT-HANDEDNESS*

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If he then tries to form his own opinion by testing and observing his patients he soon finds that his decision whether a given child is right-handed, left-handed or ambidextrous often depends on the number and type of tests used. If his bias is toward a comparatively large number of ambidextrous subjects, all he need do is administer a large battery of laterality tests that include the relatively unskilled activities. On the other hand, a smaller battery testing chiefly the skilled activities will give less evidence of ambidexterity and more of definite right-handedness or left-handedness. There are many exceptions, but by and large the more tests that are given and the more the untrained activities are included the greater the amount of mixed or confused dominance that will be found.

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UNILATERAL HANDEDNESS

At the present time the adult civilized world is approximately 95 per cent right-handed. The origins of this preference for the right are lost in prehistoric antiquity, and no theory accounts satisfactorily for the observed fact. The various hypotheses, some of them almost ludicrous in their simplicity, that attempt to explain it have been well summarized by Wile⁸ and Blau.⁹ Their reports of the agreed facts on right-handedness and left-handedness may be summed up as follows:

Archeologists have demonstrated that the amount of left-handedness has diminished from the dim past to the present. Implements dating from the Stone Age are reported to show that about 50 per cent were chipped or flaked for left-handed use. Only about 25 per cent of the weapons and tools from the Bronze Age were so fashioned, and at present no more than about 5 per cent of civilized peoples are left-handed.

Anthropologists report that there is more left-handedness among contemporary primitive races than among cultured, tool-using men.

Finally, there is a steady diminution in the frequency of left-handedness from infant to adult. Roughly 20 per cent of kindergarten children, 10 per cent of school children, and only 5 per cent of adults are reported to be left-handed.

RIGHT-HANDEDNESS DUE TO ENVIRONMENTAL PRESSURE

This steady increase of right-handedness with proportionate decrease of left-handedness — from the Stone Age to the present, from living primitives to cultured peoples and from child to adult — is convincing evidence of the importance of environmental pressure in determining ultimate handedness. As stated above, however, no theory accounts satisfactorily for the fact that this pressure is always in favor of the right. Whatever the original reason, the child of the present day has to live in and conform to a right-handed world.

THEORETICAL CAUSES OF LEFT-HANDEDNESS

Environment alone, however, does not explain the whole picture because it does not account for the persisting existence of a small proportion of left-handed adults. Some believe, without completely convincing proof, that left-handedness is inherited according to the Mendelian law. Others argue that it is acquired as the result of one of the following causes: temporary disablement of the right hand during childhood before the pattern has been firmly set, imitation of left-handed siblings, parents or other adults, deliberate training of a child's left hand by adults who mistakenly believe that because he is using his left hand about as much as his right he is going to be left-handed and help him to become so, and accidental training of the left

hand by an adult who when facing a child becomes confused himself between left and right. To these Blau⁹ adds childhood negativism, — the urge to act contrary to precept and to the example of the majority, — which he believes is responsible for most left-handedness. His argument is interesting although not wholly convincing and leaves the reader with the impression that negativism may account for some but surely not all left-handedness.

CHARACTERISTICS OF LEFT-HANDEDNESS AND AMBIDEXTERITY

The presence of left-handed and ambidextrous persons in a predominantly right-handed world has puzzled the curious ever since the days of the invasion and settlement of Palestine by the ancient Hebrews.¹⁰ Although the problem of their persisting existence may seem purely scientific or theoretical, it has its practical aspects as well.

A tendency toward ambidexterity appears to be more important in this connection than left-handedness itself. The strongly right-handed or left-handed person is not particularly prone to "specific" language disturbances,* which occur more frequently among the partly ambidextrous, regardless of whether they use the right hand or the left for most activities. Unusual aptitude with the nonpreferred hand is more common among left-handed than among right-handed people, as is obvious when one considers that all mature sinistrals use the right for shaking hands, many for eating, and some even for writing. Partial ambidexterity, rather than left-handedness itself, thus seems to be the important factor associated with these language disabilities.

Ambidexterity implies a mixed or varying cortical dominance, the left cortex taking the lead in some activities and the right in others. The nerve cells that are active in controlling language are, with rare exceptions, in the left cortex in right-handed and the right cortex in left-handed persons. Unfortunately, the only practical way to locate the functioning language center in normal persons is by inference from the patients' handedness. When that is confused or uncertain one is left in doubt. Orton¹¹ and others argue that lack of clear cortical dominance is the cause of the specific language disabilities. Although absolute proof of this hypothesis is lacking, it seems very clear that there is some relation between a tendency toward ambidexterity and comparative weakness in the use of language.

Left-handedness and ambidexterity are also more common among children, the mentally retarded, criminals and geniuses. This does not mean that they are causes of these conditions. Children are still in the original state of using both hands fairly equally, the mentally retarded, in this as in most respects, are still children, some criminals fall into

*Motor speech delay, infantile speech stuttering and specific reading disability are regarded as specific language disabilities.

the same group, whereas others seem to exemplify Blau's theory of a negativistic attitude toward the world, and geniuses by and large are extremely individualistic and hence more likely than the average to resist successfully the external pressures toward right-handedness

THEORIES OF LEFT-HANDEDNESS AND AMBIDEXTERITY

Of the many theories propounded to account for the existence of left-handedness and ambidexterity in a right-handed world, none have been widely accepted. In general they repeat with variations the old and endless dispute between the champions of heredity and of environment. Simply stated, the unsolved question is whether right-handedness and left-handedness are inherited as such or are acquired after birth as a result of imitation, training, and social and cultural pressure. In such a complex human skill as unilateral handedness, it seems likely that both factors are usually involved.

FLUIDITY OF HANDEDNESS IN THE INFANT AND SMALL CHILD

Right-handedness and left-handedness in the usual sense of the terms are absent in infancy. A baby has no particular skill with either hand and, as Blau⁹ states, should be classed as ambilateral rather than ambidextrous. Giesecke¹ reports that from a few hours after birth one hand is more active than the other and that later this more active hand is the one chosen for reaching and grasping. Gesell² has shown that more frequent use of a particular hand for reaching and grasping does not begin until the infant is at least sixteen weeks old. Throughout infancy this more frequent use of one hand should not be taken to mean that it is the dominant or master hand in the adult sense; it indicates merely that it is the preferred hand for the time being.

The truly skilled and leading hand does not appear for several years. In fact, as Giesecke,¹ Gesell² and others^{3, 4} have demonstrated, the most used hand shifts from side to side at fairly regular intervals for a number of years. Gesell states that an infant passes through definite phases of being right-handed, left-handed and bilateral. He has reported a number of children who were apparently right-handed at two years and equally left-handed at three years, before becoming finally and permanently right-handed at five years. Evidently it is not until habitual use of one hand over a long period has given that hand definitely superior skill that it is fair to describe its possessor as a right-handed or left-handed person.

Unless this normal variation of handedness in infancy and early childhood is kept constantly in mind, laterality tests of young children may be extremely misleading. Certainly no definite or final

conclusion about a person's ultimate handedness should ever be drawn from them.

INHERITANCE AS A CAUSE OF HANDEDNESS

The influence of environment on handedness has been shown. It seems very certain, however, that this is not the only factor concerned. Some cases of left-handedness and ambidexterity appearing in the same family over several generations may undoubtedly be ascribed to environment. In many others, however, the left-handed relatives were so widely separated in time or space that imitation could not have been responsible for their occurrence. One is therefore forced to admit that inheritance may also play its part in determining the final result.

Until fairly recently those who believed in the inheritance theory were forced to assume something in the genes that led to the eventual dominance of the left or right cerebral cortex and so to right-handedness or left-handedness. Their opponents meanwhile insisted that it was the more frequent use of the preferred hand that established dominance in the appropriate cortex.

A clue to how heredity may affect handedness has been suggested by Gesell.² He has traced back into fetal life a basic trend toward the final adult handedness by demonstrating a relation between the preferred tonic-neck-reflex position of the premature infant and his ultimate handedness. Since the tonic neck reflex develops as early as the twenty-eighth week after conception,¹² it seems impossible that environmental pressure after birth can do more than modify a fundamental tendency.

TONIC NECK REFLEX OF THE HUMAN INFANT

When a normal newborn infant turns his head to one side, the arm and leg on that side automatically straighten and extend themselves, the opposite arm bends toward the head, and the opposite leg flexes at the hip and knee. Equally automatically, this position reverses itself when the infant turns his head the other way. This obligatory response to the turning of the head is known as the tonic neck reflex.

It is present in typical form in all normal newborn babies, fading gradually and becoming replaced by symmetrical arm and leg movements by the time the infant is twenty weeks old. Its presence at an older age indicates serious disease of the brain.¹³

NEUROMUSCULAR DEVELOPMENT IN THE SALAMANDER EMBRYO

An example taken from a lower form of life is illuminating. Coghill¹⁴ succeeded in correlating the behavior of the amblystoma embryo at different stages of development with the growth of its nervous system. His account is fascinating and too little known among physicians.

At an early stage the embryo lies motionless and does not respond to stimulation. A little later it spontaneously "bends itself into a tight coil . . . [which] may be reversed instantly into a coil in the opposite direction." The flexing motion begins at the head and progresses caudad.

The next stage is the appearance of a second flexion of the head in the opposite direction before the first has reached the tail. These flexions, when better co-ordinated and more rapid, result in forward motion of the embryo, as in swimming. When the forelimbs are sufficiently developed, the one on the concave side is adducted, and the one on the convex side is abducted during flexion of the neck and trunk. These movements are the beginnings of forward motion of the body on land, as in walking.

Coghill demonstrated conclusively that the co-ordination of these flexions into swimming movements depends upon the growth of connecting cells in the floor of the medulla and in the upper part of the cord. "The growth of terminals of nerve cells over a distance of less than 1/100 of a mm transforms (the animal) from (one) that must lie helpless where chance has placed it into one that can explore its environment."

RESEMBLANCE BETWEEN SALAMANDER AND INFANT

There is a striking similarity between Coghill's drawings of *amblystoma* illustrating the beginning of walking and Gesell's photographs of infants in the tonic-neck-reflex position. The resemblance is so marked that it seems extremely likely that they represent approximately equivalent stages of development of the nervous systems of the two species.

RELATION OF THE TONIC NECK REFLEX TO HANDEDNESS

Gesell² reports that the great majority of infants when in the tonic-neck-reflex position spend more time with the head turned to the right than to the left. He followed 10 infants with predominantly right tonic neck reflexes for ten years and found that they all became right-handed children. He followed 9 with predominantly left tonic neck reflexes for the same period and found that 4 became left-handed and 5 right-handed. He is careful to draw no conclusions but merely comments that, although the tonic neck reflex is usually indicative of later handedness, there are interesting and significant exceptions.

He states that the strength and persistence with which the tonic-neck-reflex position is held varies greatly in different infants. It would be interesting to know if the 5 infants with left tonic neck reflexes who grew up to be right-handed were relatively weak in their tonic neck reflexes. Whether they were or not, and it seems likely that they were, it appears very probable that the 5 who changed from a predominantly left tonic neck re-

flex in early infancy to right-handedness in later childhood did so in response to environmental pressure. It is not wholly clear why the remaining four did not change also. It may be that their preference was unusually strong, or it may be that they were influenced by some of the secondary factors mentioned above.

DISCUSSION

Obviously, an answer to the question whether or not it is safe and wise to train an apparently left-handed child to write with his right hand cannot be unequivocal.

It has been pointed out that there are two entirely different kinds of handedness in early childhood: one is physiologic, native, inherent, inherited, and the other is psychologic, acquired, environmental, cultural. The first is the tendency — strong in some, weak in others — to prefer to use for more difficult manipulations a particular hand, which may be either the right or the left. Apparently, from a number of reports, this tendency is never absolute, but instead shifts normally from side to side throughout infancy and the early years of childhood, often with only a relatively slight and decidedly temporary preference for one or the other hand. In most infants, however, and for most of the time, Gesell reports that the right hand is more frequently used.

The second kind of handedness, in contemporary civilization at least, is the product of a steady, rather strong, social and cultural pressure favoring the use of the right side. There is no satisfactory explanation of why in the present day the right hand is always "right." One must accept that as a fact, although there are some indications that, in other times and civilizations, the left was the preferred side.⁹

In the older child and in the adult the eventual and permanent handedness appears to be the outcome of the merging of these two influences. Environmental pressure toward the right merely strengthens and confirms native right-handedness. When the inherent tendency is toward the left it comes into direct conflict with the environmental right. The result then seems to depend upon the relative strengths of the two opposing tendencies. When the inherent left preference is strong it is able to resist more or less completely the external pressure toward the right. This situation probably accounts for the majority of left-handed persons and for those who are left-handed with some right-handed skills. When the inherent left tendency is weak, it is largely or entirely overcome by the external right, producing persons who are either wholly right-handed or right-handed with some left-handed ability.

The groups of right-with-some-left and left-with-some-right are usually classed as ambidextrous. This is an ambiguous term with no very satisfactory definition. It is generally agreed that there is no

such condition as complete or absolute ambidexterity, in the sense that both hands are equally capable in all activities. All ambidextrous persons are right-handed in shaking hands, most are in eating, and some even are in writing. What is really claimed for them is that they choose the right hand for some activities and the left for others, or else that, although apparently right-handed or left-handed, they can perform most tasks better with the nonpreferred hand than the average person can. Consequently, except for the fact that the term is firmly imbedded in the language, it would be better to abandon entirely the classification of "ambidextrous" and replace it with such terms as right-with-some-left and left-with-some-right, which come much nearer describing the actual conditions.

It should by now be clear that the safety and wisdom of teaching an apparently left-handed child to use his right hand for writing depends upon the strength of his inherent preference for the left. If this preference is strong, or if for one reason or another he has become accustomed to use his left hand for all skilled acts, to force him to wield a pencil with his right may be difficult or even impossible. Conversely, if he is already using his right hand for some activities, he may probably be taught to write with it without difficulty.

It is only rarely that the question arises of shifting an older child from right-handed to left-handed writing. It should never even be considered unless he is strongly left in other activities, is having difficulty in expressing himself orally or on paper and is wholeheartedly ready and willing to try the experiment. A number of cases have been reported in which the shift was made with beneficial results, but they certainly are not common and the change should never be advised without considerable thought.

The chances of producing stuttering by teaching an apparently left-handed child to use pencil and pen with his right hand have probably been exaggerated. When stuttering does develop under these circumstances it is as likely to indicate an inherent weakness of the speech mechanism that causes it to break down under any added strain as it is to mean that the speech center has been partly shifted to the originally nondominant side of the cerebral cortex. The latter hypothesis is an attractive one, but it

has never been satisfactorily proved. The experience of many primary schools has shown that in most cases apparent left-handers learn to use the right hand for writing without suffering any disturbance of speech.⁹

CONCLUSIONS

Many apparently left-handed primary grade children may be successfully taught to write with the right hand. When writing begins they should all be so taught, because the use of the right hand fits in better with the left-to-right direction of writing and also because it conforms to the custom of the majority and hence is easier psychologically. If, however, a child objects strenuously or develops signs of nervous strain, of which stuttering may be one, the attempt should be abandoned at once, and he should be allowed to use his left hand without criticism.

Those who are taught to write with the left hand should be shown the proper position of the paper, which is slanted with the top border to the right instead of to the left as is usual. It is often necessary to drill them in the use of this position, since otherwise they are likely to imitate their right-handed neighbors. They should also be allowed to write with a slight backhand slant if they so prefer.

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EPIDERMOID CARCINOMA PRIMARY IN BARTHOLIN'S GLAND

JOHN F CURRAN, SR, M D,* AND THOMAS V HEALEY, M D †

WORCESTER, MASSACHUSETTS

CARCINOMA of Bartholin's gland is one of the rarest malignant lesions occurring in the female genital tract, approximately 75 cases having been reported in the literature. In 1939, Simendinger,¹ with a detailed résumé of 38 cases, enumerated and classified the cases since Klob's² initial reference to the lesion in 1864. Isolated reports have subsequently appeared in the surgical literature,³ and Boughton,⁴ in a scholarly review of the problem in 1943, adjudged that by that time 75 cases had been listed, but that "a great number of these are published with inadequate data and may not be accepted as proved cases of Bartholin's gland carcinoma." Throughout such studies as have been cited and in more recent case reports,^{5, 6} there has occurred a major preponderance of adenocarcinomas as compared to epidermoid neoplasms. Furthermore, in Taussig's⁷ series of 155 cases of vulval cancer, only 9 originated in the vulvovaginal gland, similarly, in the files of the Worcester City Hospital, there are records of only 2 vulval neoplasms and 1 of the vestibular gland. Because of the relative infrequency and paucity of epidermoid types of tumor of this gland heretofore reported, we have been prompted to describe a case of epidermoid carcinoma primary in Bartholin's gland, which was recently treated on the wards of the East Surgical Service in the Worcester City Hospital under the supervision of one of us (J F C).

INCIDENCE

The incidence of this lesion has been established between the ages of forty to fifty-five years, whereas etiologic factors have been sought in chronic irritations and infections, trauma of sexual intercourse and tertiary syphilis.^{8, 11}

PATHOLOGY

Histologically, there are two types of carcinoma of Bartholin's gland: adenocarcinoma and epidermoid carcinoma. These forms are possible because the acini are lined by cuboidal cells, and the superficial ducts near the surface are lined with stratified squamous epithelium. The ducts lying between the acini and the superficial squamous-lined ducts are lined with a transitional type of epithelium, which readily undergoes metaplasia.¹²⁻¹⁴ Honan¹⁵ has expounded certain criteria necessary for a diagnosis of cancer primary in Bartholin's gland to be entertained. Extensive search of the literature reveals no special study of the lymphatics

that drain Bartholin's gland, they are generally considered to be the same as those from the vulva, with a predilection for the inguofemoral chains bilaterally because of the lymphatic anastomosis in the mons veneris.⁴ However, no cases of bilateral involvement of these glands have been reported. Such an extension to the inguofemoral nodes occurs with rapidity and prognosis is unfavorable, chiefly because early diagnosis is infrequent.¹⁶ A five-year-period without recurrence is not long enough to establish cure, since recurrence may take place ten to eighteen years after operation.¹⁷

SYMPTOMATOLOGY

The growth is sometimes first noted as a small, firm, nodular, painless swelling in the normal position of Bartholin's gland. At the beginning, it may be mobile, but later as the growth extends, it infiltrates the surrounding tissue and becomes fixed.¹⁰ Enlargement of the growth is attended by pain, which is commonly referred to the coccyx and groin and is made worse by coitus and menstruation. Walking may become painful, and a fetid leukorrhea with a serosanguineous discharge from the duct of the gland may develop. As the overlying skin becomes involved in the tumor mass, the growth becomes reddened, edematous and painful to touch. With continued progression there is a tendency for the mass to become necrotic, so that the tumor may feel fluctuant and may be confused with a cyst. The neoplasm tends to grow deeper rather than more superficially and involves the surrounding fat, the muscle tissue and, later, the pubic bones.

PHYSICAL FINDINGS

Usually there is a hard, nodular swelling situated to one side of the introitus, with an intact, overlying skin surface. The labium majus pudendi may be increased in size, especially in its posterior part. The tumor is felt in the portion of the labium corresponding to the normal site of the vulvovaginal gland, and it is usually lobulated on palpation. The mass is mobile and painless on pressure, and the suprajacent skin is normally free of the growth. There may or may not be inguinal adenopathy. Diagnosis is established by consideration of the possibility of carcinoma, failure of response to conservative measures and biopsy.

TREATMENT

Proper therapy of this disease appears to be a combination of irradiation and surgery,¹⁸ although

*Senior surgeon East Surgical Service Worcester City Hospital

†Assistant surgical resident East Surgical Service Worcester City Hospital

clinicians are not unanimous in opinion and no one surgeon's experience has been wide enough to outline a definitive course of treatment. Some advocate radical vulvectomy, including excision of the labia minora and clitoris by electrocoagulation supplemented by the extirpative inguinofemoral-lymph-node dissection of Basset bilaterally. Taussig¹⁹ recommends that this procedure be done in two stages: excision of the vulva, followed in two weeks by the groin dissections. Others reverse this order, employing the gland dissections first, always including removal of the so-called gland of Cloquet lying within the femoral ring in juxtaposition to the femoral vessels. Still others insist on preoperative and postoperative irradiation as a vital part of the treatment. Te Linde¹⁸ states that, in his opinion, irradiation should follow the radical operative procedures to give the patient every chance for recovery from a disease in which the prognosis, regardless of treatment, is poor.

CASE REPORT

L. H. (W. C. H. 371197), a 37-year-old divorced woman, was admitted to the hospital on April 16, 1948, with the complaint of "a small lump" on the right labium majus pudendi of about 5 years' duration. For the last year, the mass had been increasing in size and had of late been painful enough to cause her to seek medical advice in the outpatient department. Thence, she had been referred to the hospital with a presumptive diagnosis of "chronic Bartholin's cyst on the right." History elicited by the admitting house officer revealed that the tumor had been increasing in size of late, on two occasions had discharged bloody fluid and at times had caused pain in walking. There was no radiation of the pain, and the only other time the growth caused distress was if she inadvertently compressed it at toilet.

A review of the systems was noncontributory.

The menarche had begun at 11 years of age, the periods were irregular and of 7 days' duration without clots. Pain was marked for the first day. There was no intermenstrual discharge since an oophorectomy in 1938, the periods had occurred but once or twice yearly.

Physical examination revealed an obese woman with a pronounced alcoholic odor to the breath lying quietly in bed in no acute distress. There was a generalized psoriasis over the body. Physical findings of note were limited to the local examination: a firm, indurated, tender mass the size of a grape, situated to the side of the posterior fourchette in the position normally occupied by Bartholin's gland. No discharge could be expressed from the gland through its duct. The mass was tender, causing exquisite pain on palpation, and was reddish purple, with whitish areas shining through from deeper within the mass. It was nonfluctuant and mobile, although the overlying skin was firmly adherent. There was no demonstrable inguinal lymphadenopathy.

The temperature was 98.6°F, the pulse 88, and the respirations 20. The blood pressure was 136/82.

Examination of the blood disclosed a hemoglobin of 91 per cent and a white-cell count of 4800 with 66 per cent neutrophils, 4 per cent eosinophils, 1 per cent basophils, 26 per cent lymphocytes and 3 per cent monocytes. Blood Hinton and Kahn tests were negative. A chest film was unremarkable. The fasting blood sugar was 87 mg, and the nonprotein nitrogen 31 mg per 100 cc.

At operation on April 21 under nitrous oxide, oxygen and ether anesthesia a pelvic examination, precluded because of tenderness of the mass on admission, was performed without remarkable note. An elliptical incision was described about 0.6 cm around the cystic mass, which was then grasped with an Allis clamp and elevated. The mass was excised with intact overlying skin and a considerable amount of subadjacent areolar tissue. It was not possible to identify the duct to the gland.

The pathological diagnosis was epidermoid carcinoma (Grade II), primary in Bartholin's gland. The overlying skin was reported as normal and intact. The patient was seen in consultation by members of the Radiology Department, who believed that at this stage surgery should be relied upon solely to grant the patient a cure. A roentgenogram of the pelvis and pubic rami showed no evidence of metastatic involvement.

On April 30, under spinal anesthesia, the labia majora, mons veneris, clitoris and labia minora were excised generously with the cutting current of the electrosurgical knife. Hemostasis was secured with electrocoagulation and No. 4 to 0 catgut ligatures where needed. The skin was then sutured directly to the vaginal mucosa, and superiorly over the pubic arch, skin was sutured directly to skin in a vertical manner, although it was under some tension. An inflating Foley catheter was introduced to compensate for urethral edema and consequent urinary obstruction. Recovery was uneventful, the catheter being removed in 5 days with ensuing normal vesical function.

The pathological diagnoses were specimens consisting of labia majora, labia minora and clitoris and acute inflammation of recent incisional site.

At operation on May 14 under spinal anesthesia, a right-sided Basset operation was performed, with opening of the inguinal canal, removal of the round ligament, division of the inferior epigastric vessels and dissection for iliac, inguinal and femoral lymph nodes. No Cloquet node was detected, but several were removed from the iliac vessels. After operation, the patient was placed on anticoagulant therapy as a prophylaxis against femoriliac phlebitis, the blood prothrombin time being maintained at about 40 per cent of normal. The subsequent clinical course was without incident, and sutures were removed on the 9th postoperative day.

The specimen consisted of fascia and muscle tissue. The lymph nodes showed chronic lymphadenitis.

On May 28, under spinal anesthesia, a Basset operation was carried out on the left side as described above. Several lymph nodes were removed from the iliac chain, but again no Cloquet node detected. The patient was again placed on an anticoagulant regime for several days and convalesced without incident. The skin sutures were removed on the 7th postoperative day.

The specimen consisted of areolar tissue, fascia and muscle. The lymph nodes showed chronic lymphadenitis.

The patient was seen again in consultation by the Radiology Department, which preferred not to administer radiation but rather to follow the patient in the Tumor Clinic. Pelvic examination on the day of discharge showed an introitus readily admitting two fingers, with well healed suture lines. The patient was discharged on June 4, to be followed in the Tumor Clinic.

SUMMARY

A case of epidermoid carcinoma primary in Bartholin's gland is reported, and the literature on the subject is reviewed.

The epidermoid types of tumor of this gland are rare.

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MEDICAL HAZARDS ASSOCIATED WITH THE FISH INDUSTRY IN MASSACHUSETTS

JOHN B SKINNER* AND CLARENCE C MALOOF, M D †

BOSTON

THE fish industry in Massachusetts is quite extensive and is to be found primarily near Cape Ann, in Boston and around New Bedford. The principal fish brought to these ports include cod, haddock, mackerel, herring, redfish, pollock, whiting, sole and flounder. The fish may be processed for sale in a number of ways. They may be sold in a fresh state round, dressed or filleted, they may be frozen whole, dressed or filleted, they may be prepared for canning, and they may be salted, although this treatment is becoming obsolete.

In the processes in which fillets are obtained, the fish is first descaled by passing through an inclined rotary tumbler with holes in the periphery. The descaled fish is filleted by workers grasping the fish by the head and cutting strips of meat from either side. The fillets are washed, packaged and frozen or packed into cans, which are capped, sterilized and washed in a cleansing solution to remove oil or fragments of fish.

The offal derived from fish is usually called "gurry" and is used primarily for the preparation of fish meal for chicken and animal feed, fish oils for animal feeding and industrial uses, and glues. The "gurry" consists of all portions unsuitable for eating, such as the head, fins, tails, skins, entrails and scales. Some of these manufacturing processes involve considerable handling of the "gurry," frequently with a resulting dermatitis.

One of the most serious health hazards in the fish industry is dermatitis. This falls into several categories. Although salt is used in salting fish and is usually handled with the bare hand, unless the worker is suffering from skin abrasions, it apparently does not cause dermatitis. The alkali used in washing the sealed cans to remove oil or fragments of fish occasionally causes skin irritation. However, dermatitis actually due to the handling

of the fish is mostly confined to the so-called "red-feed" dermatitis. This occurs only from June to September when mackerel are in season. The mackerel feed on minute crustaceans, one of the most common of which is "redfeed." The fish containing "redfeed" do not keep well after being caught. A few hours later the flesh of the fish opens, and after twenty-four hours the flesh is broken down to the spine. Hydrogen sulfide is rapidly evolved from such fish. The "redfeed," in addition to the digestive juice from the stomach of the mackerel, may cause a dermatitis to appear after one or two days' exposure. The skin, generally of the hands, becomes swollen and intensely red, with numerous superficial ulcerations. The areas affected are those in contact with the "redfeed" and occur chiefly along the palms and the sides of the fingers. Although the lesion is painful, it heals quickly upon application of mild soaks, such as boric acid or dilute epsom salts, followed by boric acid or zinc ointment, and avoidance of further contact with the material.

TUNA

The skin of the tuna is a thin, slimy membrane covering the scales, which can easily be scraped off and is said to contain a substance that is a primary skin irritant. It will cause dermatitis in anyone working for any length of time with ungloved hands.

REDFISH

Puncture wounds are extremely common when the workers handle redfish, which are usually filleted for quick freezing and principally sold in the Midwest. The worker grasps the fish in his left hand by the head, and with a stroke of the knife cuts off the boneless material on either side. Because of the fact that the redfish has numerous pointed bones extending back from its head, a puncture of the skin may occur if the fish is not held firmly. These puncture wounds are sometimes

*Director, Division of Occupational Hygiene, Massachusetts Department of Labor and Industries.

†Physician, Division of Occupational Hygiene, Massachusetts Department of Labor and Industries.

followed by lymphangitis and lymphadenitis, occasionally resulting in suppuration of the involved lymph nodes

ERYSIPELOID

A skin lesion frequently seen along the Atlantic Coast is erysiploid. It occurs primarily from contact with the "gurry" or the remains of any fish that has undergone putrefactive changes. In the handling of "gurry," abrasion, laceration or puncture of the skin is common, and erysiploid may result. This has been demonstrated to be caused by the organism *Erysipelothrix rhusopathia*. Of the 100 cases analyzed by Klauder,¹ 88 were occupational in origin, and 17 occurred in persons handling fish.

There is always a history of injury, and usually one of puncture of the skin by a fish bone. Erysiploid may develop within several hours to one or two days. The lesion is always on the hand and appears first at the site of puncture, where there is moderate pain followed by swelling and redness. The erythema progresses down the fingers into the web and frequently spreads along the adjoining finger. Swelling may be severe, interfering with function. Arthritic symptoms sometimes occur, and they may persist after the cutaneous lesions disappear. Lymphangitis is frequent, and many of the workers complain of pain and tenderness along the arm and forearm. Occasionally, there is a mild rise in temperature.

WEIL'S DISEASE

Another occupational disease experienced by fish cutters is Weil's disease or spirochetal jaundice.² The fish may become infected through the urine of infected rats. This disease is acquired through invasion of the organisms through the broken skin. After a varying period of several days or several weeks, the worker is aware of the onset of an acute illness characterized by chills, fever, headache, prostration and muscle and abdominal pain with nausea and vomiting. Inflammation of the eye frequently occurs, and jaundice with bleeding tendencies may appear after several days.

FISH OILS

Some workers develop dermatitis because they are allergic to fish oils. These cases are usually confined to those handling cooked fish in the canning departments.

OTHER CONDITIONS

In addition to exposure to the previously described infections, the workers are exposed to dampness, inasmuch as the fish are wet and in many cases the tables and floors of the workroom are con-

tinually wet. Exposure to dampness may result in neuralgic and rheumatic affections and may also be a contributing factor to respiratory infections. Where quick freezing of fish occurs, there is a potential exposure to refrigerants. In most cases, ammonia is used, and although the refrigerant is kept within a closed system, there is always the possibility of breaks in the piping. Ammonia is a highly irritant gas and is usually soluble in water and body fluids. It affects the upper respiratory tract, and consequently the workers immediately seek the out-of-doors when exposed to hazardous concentrations. However, if they are trapped in the room and cannot escape, they may develop a severe pulmonary edema.

In plants handling the "gurry" for conversion to animal feed, it is usually necessary to minimize the decay of the fish. In some cases, this is done by spraying the fish with chlorinated water. In other plants reliance is placed upon ozone to prevent this decay. In either case, the workers are potentially exposed to either of these two gases, which are lung irritants and should not be allowed to exist in concentrations greater than 1 part per 1,000,000 parts of air.

TREATMENT

The treatment of any of the above untoward effects is similar to that of any contact dermatitis or infection with resulting lymphangitis and lymphadenitis or pulmonary irritation with resulting pulmonary edema.

PREVENTION

The prevention of dermatitis from fish may be accomplished by the use of rubber gloves. These gloves should have treads on the finger tips to enable the workers to handle the slippery fish, or they should be covered with cotton gloves. A small amount of chlorine added to the water to wash the gloves has proved helpful in destroying contaminant organisms.

Where Weil's disease is experienced, elimination of rats is necessary. The use of protective clothing, boots and gloves minimizes skin contact with potentially infected material.

Where refrigerant gases may be encountered, the area should be well ventilated, and gas masks approved by the United States Bureau of Mines for protection against ammonia or other particular refrigerants should be available in handy locations for emergency use if leaks develop in the refrigerating system. The use of proper drains and floor boards will minimize the exposure to dampness.

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MEDICAL PROGRESS

RUBELLA (GERMAN MEASLES) AND CONGENITAL DEFORMITIES*

CONRAD WESSELHOEFT, M D †

BOSTON

THE part played by rubella in the production of congenital deformities presents a serious problem in medical practice as well as in public health. The report by Gregg in 1941 of 78 cases of congenital cataract following maternal rubella aroused the attention of the medical profession to the dangers of this disease to the fetus in the early months of pregnancy. Since then numerous studies have been carried out confirming these original findings, as well as showing that other injuries to the fetus of equal gravity may ensue. Indeed, this virus appears to be capable of bringing about a pattern of defects in this early period of fetal life, consisting mainly of damage to the eye, ear, heart, teeth and brain, and these may occur singly or in combination. The entire subject of rubella was discussed, including its history, pathogenesis and differential diagnosis, in a progress report¹ in 1947. The purpose of this paper is to present subsequent material dealing with congenital defects and to bring the subject matter up to date.

At the outset it is well to recall that rubella is a disease entity unrelated to measles, and that one attack usually confers a lifelong immunity, although second attacks may take place. No vaccine is as yet available. Drugs and antibiotics exert no influence on the virus. The diagnosis rests on those characteristics that differentiate this malady from the other exanthems—namely, the absence of Koplik spots, the kaleidoscopic character of the rash, the presence of palpable lymph nodes behind the ears and not infrequently a pink suffusion of the whites of the eyes, in contrast to the sticky mucopurulent conjunctivitis of measles. All these features are variable, depending on the severity of the disease. The circumstantial evidence of a known exposure coupled with an incubation period of approximately eighteen days is always helpful in diagnosis. The rare complications—polyarthritides, thrombopenic purpura and encephalitis—are not considered here, because neither the severity of the disease nor its complications appear to have any bearing whatever on the incidence or severity of congenital deformities. The complications that are concerned here are those of

rubella during pregnancy, and are the results of injury to the fetus in utero.

MISCARRIAGE

The virus of rubella has been isolated from the blood in the early stages of this disease. Therefore, when a pregnant woman is attacked by rubella the virus appears to be capable either of finding its way through the placenta to the fetus or of disturbing the fetal metabolism. Thus, in one way or another, certain peculiarly susceptible tissues may suffer injury. The fetus may die promptly or linger along and die several months after the attack. Death of the fetus early in pregnancy frequently results in the spontaneous emptying of the uterus. When death of the fetus occurs in the later months of pregnancy, the uterus is not so ready to empty itself and may continue to retain the dead fetus for some time without any apparent injury to the mother. Just how often spontaneous miscarriage takes place in the course of maternal rubella is unknown. Two cases in which the attack of rubella occurred in the second month with spontaneous abortion in the third month have already been reported,¹ and to this I can add a similar one. In a fourth case, in which the attack was in the second month, the patient was delivered of a macerated fetus in the seventh month.

Swan and Tostevin² reported a miscarriage in the third month following rubella in the second month of pregnancy. Goar and Potts³ described one stillbirth at seven months after an attack in the first month. Fox and Bortin⁴ discussed a stillbirth at the seventh month following rubella in the first month of pregnancy. Ober, Horton and Feemster⁵ reported 9 pregnancies that terminated in abortion or stillbirth in which the attacks of rubella were in the first four months of pregnancy in 7 cases. Indeed, in this survey conducted for the year 1943 in Massachusetts there were as many abortions and stillbirths uncovered as there were defective children. Swan⁶ has recently reported 15 cases of stillbirth following rubella, in 13 of which the infection took place within the first four months. The sum total of these reports comprises 31 abortions or stillbirths following rubella, 27 of which occurred after an attack in the first four months of pregnancy.

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From the Harvard School of Public Health and the Haynes Memorial, Massachusetts Memorial Hospitals.

†Clinical professor of infectious diseases, Harvard School of Public Health.

I am firmly convinced that any effort to prevent miscarriage during or after an attack of maternal rubella is misdirected energy, since it is not in the best interest of the mother, to say nothing of the best interest of the fetus if it is alive. To my mind, the signs and symptoms of threatened miscarriage during or after an attack of rubella should be looked upon with favor. Consultation with and confirmation by a second physician, together with the

developed gross dental defects. To this can be added 21 gross defects reported in the literature (Table 1).

NORMAL CHILDREN BORN OF MOTHERS WHO CONTRACTED RUBELLA DURING PREGNANCY

There have been reported 36 additional normal babies born of mothers who suffered an attack of rubella during pregnancy: 11 in the first, 17 in the

TABLE 1 *Severe Congenital Deformities among Children after Rubella in Pregnancy*

SOURCE	TOTAL CASES 521	EYE DEFECTS 221	DEAFNESS 243	HEART LESIONS 221	MICRO-CEPHALUS 74	MENTAL RETARDATION 24	DENTAL DEFECTS 20
Wesselhoeft ¹							
First Quarterly Report National Society for the Prevention of Blindness and American Academy of Pediatrics ⁷	114	76	55	67	22	46	2
Ober, Horton and Feemster ⁸	5	3	1	4	1		
Sanderson ⁹	1			1			
Pirrie ⁹	1	1	1	1			
Friedman and Cohen ¹⁰	1	1			1	1	
Ingalls and Davies ¹¹	3					3*	
Buffington ¹²	2	1		1			
Bass ¹³	6	6		1		5	
Wesselhoeft (1948)	2	1	1				
Totals	656	310	281	296	98	79	22

*Mongolism.

written consent of the parents, is all that is required for legal protection in carrying out the surgical emptying of the uterus.

SEVERE CONGENITAL DEFECTS FOLLOWING RUBELLA IN PREGNANCY

In the progress report mentioned above I recorded from the literature 521 major congenital defects after an attack of rubella in pregnancy, as

second, and 8 in the last trimester. This gives a total of 656 defective infants as against 124 normal babies, a ratio of 5 to 1 (Table 2).

As pointed out in the previous progress report, this figure cannot be taken as the true ratio of grossly defective infants to normal babies of mothers who had rubella in pregnancy. The two sets of figures are obtained without relation to each other. Therefore, the ratio cannot be construed

TABLE 2 *Normal Babies Born to Mothers Who Contracted Rubella during Pregnancy*

SOURCE	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	TOTALS
Wesselhoeft	2	7	8	6	5	7	5	4	4	48
Ober et al. ⁸	1	4	6	5	9	5	6		2	36
Totals	3	11	14	9	14	12	11	4	6	84
				First Trimester		Second Trimester		Third Trimester		
				28		55		21		
Prendergast ¹⁴				4*						
National Society for the Prevention of Blindness and American Academy of Pediatrics ⁷				11		17		8		
Totals				43		52		29		124

*First trimester only investigated

against 52 reports of normal babies following this disease in pregnancy.

Since then the first quarterly report of the committee appointed by the National Society for the Prevention of Blindness and the American Academy of Pediatrics⁷ gives the following additional data on 132 mothers who had rubella during the first trimester of pregnancy. Among these there were 18 normal babies. Seventy-six babies had congenital cataracts, 35 were completely or partially deaf, 67 had congenital heart lesions, 46 were mentally retarded, there was 1 cretin and 1 mongolian idiot, and 22 were microcephalic. Two

as the risk. Nor can the risk be properly calculated on the basis of reported cases, since it has been estimated that only 14 per cent of cases are reported¹⁵ and congenital deformities are not reportable. The backward approach to this whole subject renders any mathematical calculation open to serious objection. The total score presented here merely represents a danger to the fetus when rubella occurs in the course of pregnancy — a danger that apparently is greatest in the first trimester as was clearly brought out in the first report of Swan et al.,¹⁶ and confirmed by subsequent reports.

It has been shown that congenital cataract of the central and nuclear type and certain congenital anomalies of the heart, such as interventricular septal defects, result from defective development in the first trimester^{1 17} Mongolism follows arrested development taking place between the sixth and ninth weeks¹¹ Thus, the stage of development of the fetus at which the agent is active determines the type of injury that may take place The records of the cases of congenital defects following rubella in pregnancy when the time of the attack of rubella is given in relation to the stage of pregnancy are in agreement with this knowledge of embryology established prior to 1941 and in conformity to more recent studies with trypan blue, which does not reach the fetus¹⁸ An interesting feature in all this speculation is that maternal rubella just prior to conception,¹ as well as an injection of trypan blue to the mother rat prior to conception, can result in congenital deformities¹⁸

Thus, the virus in maternal rubella in some manner, either directly or indirectly, shows a predilection for injuring certain tissues in the fetus according to the stage of fetal development It is not understood just how the arrest of development in these organs is brought about although much theorizing is done on this subject The fact that damage takes place in accordance with known embryologic expectancy offers supportive evidence that one is dealing with an agent that can produce predictable consequences However, as in other infections there is always the unpredictable element of the resistance of the tissues in the host, which allow of great variability in the injury done — from complete escape to multiple serious injuries and even death Thus, the predictable consequences of maternal rubella on the fetus are merely possibilities, which become more likely according to the age of the fetus at the time of the rubella attack So far as the first four months of fetal life are concerned the information to date suggests a very real danger that maternal rubella may result in a serious congenital defect

Therapeutic abortion is immediately challenged by two objections The first is that insufficient data are at hand to warrant considering therapeutic abortion The figures obtained by Fox and Bortin⁴ and Ober et al⁵ purport to show that the risk of congenital deformities is much less than one gathers from other surveys and the total reported congenital deformities and normal births following rubella As already stated, these data are obtained from records that are too imperfect to be reliable The evidence against rubella, though largely on an empirical basis as yet, is sufficient to make one aware of a danger to the fetus in early pregnancy This danger to the life of the fetus is not nearly as disastrous in its consequences as it is to the welfare of the family in the event of survival with gross congenital deformities

The second objection is that therapeutic abortion, except to save the life of the mother, is not permissible by law in Massachusetts The legal aspects of this situation were discussed at length in the previous progress report¹ The statutes regarding abortion vary in different states, and not only has the fundamental law undergone changes whereby a later proviso permits a therapeutic abortion to save the life of the mother but also judicial opinion regarding this proviso offers a broadened interpretation to permit the emptying of the uterus beyond the danger to the mother's life The law and medicine are subject to change in social evolution The purpose of both is to protect and benefit mankind Consequently, when some new development in the knowledge of medicine reveals any legal obstruction to the carrying out of a desirable preventive measure for the benefit of mankind due consideration should be given to the enactment of modifying statutes to meet the situation

It is of the utmost importance to stress the fact that the birth of one of these grossly deformed babies is not simply a disaster to the individual child but that such a grossly deformed child tends to blight the life of the entire family The mother has to give so much attention to this child that she becomes worn out in body and mind As a result of this the other children in the family fail to get proper care Furthermore, social-service follow-up studies show that the parents of such a defective child are often afraid to have any more children, even when it is explained to them that this will not happen again They say that they just could not take on the care of another infant — even a healthy one This attitude is expressed in various economic walks of life In short, the arrival of a grossly defective child in a family not only brings unhappiness and sorrow but also definitely inhibits childbearing

With all this in mind the medical profession must give attention to the danger of rubella in early pregnancy It behooves physicians to investigate this problem with the same zeal that is being shown today in the study and control of other diseases The fear of a crippling disease such as poliomyelitis makes it possible to arouse the interest and generosity of the public The accumulation of evidence against rubella as a cause of gross congenital deformities is capable of arousing fear similar to that of poliomyelitis, and like poliomyelitis, the basis of this fear is not of death but of the serious crippling defects It seems, therefore, that the medical profession must through its own initiative and with the support of public opinion take up this problem of rubella in a concerted drive under a national commission, rather than by sporadic local investigations The results of such a national investigative organization would in the course of time evaluate the dangers of this disease in their true light with satisfactory figures Along with this would be well conceived investigative work directed

toward the possibility of widespread immunization. Until work of this kind is carried out on a national scale physicians must face the problem as it lies before them today.

First of all, it becomes obvious that it is advisable for everyone to have rubella in childhood and thereby to acquire a relative, lifelong immunity. This proposition is all very well, but many children have mothers who have never had the disease and who are in the first months of pregnancy. Therefore, to encourage the spread of the disease in childhood may well increase the incidence of the disease among these pregnant mothers. Consequently, the only satisfactory solution will be an immunizing agent that does not carry with it the infectiousness of the disease itself. This has already been successfully accomplished in two virus diseases — namely, smallpox and yellow fever.

In the second place, pregnant mothers should avoid exposure to rubella. This is likewise beset with difficulties because rubella is infectious before the rash appears. For example, in the case of a woman in the first four months of pregnancy with a negative rubella history who has spent the afternoon with a friend who comes down the next day with a typical rubella, would gamma globulin do any good as a preventive measure? Theoretically, one might expect some benefit, but unfortunately gamma globulin is made from pooled blood very weak in antibodies to rubella in contrast to its content of measles antibodies. Ordinary gamma globulin has not proved effective in preventing rubella, mumps or chicken pox. The Massachusetts Department of Public Health urges physicians not to use gamma globulin except for diseases in which it has proved to be efficacious. In the case alluded to, the administration of 10 cc of gamma globulin offers only a remote possibility of protection. If the pregnant mother already has rubella, it is hardly likely that any antibodies contained in the gamma globulin could be relied upon to protect the fetus. To my mind, in the light of present knowledge of gamma globulin, its use under these circumstances offers a false sense of security.

Barring the favorable event of a threatened miscarriage, which can lead to spontaneous or surgical emptying of the uterus, physicians in Massachusetts are placed in a medicolegal dilemma. The use of

contraceptives for the prevention of disease is permitted by law. The idea of a second amendment to the law, which would permit a therapeutic abortion for the prevention of the birth of a diseased child, seems to deserve equal consideration in the interest of public health.

If all cases of rubella were reported — as they should be — and especially those in pregnant women with a note to that effect, the epidemiologic status of this disease would be better ascertained than at present, and the attendant risk of gross congenital deformities could then be satisfactorily determined. The anxiety caused by the evidence at hand regarding the danger of maternal rubella to the fetus demands that the medical profession report all cases of rubella with the utmost diligence and that the results of maternal rubella on the fetus be studied on a nation-wide basis.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

CASE 35071

PRESENTATION OF CASE

First admission A forty-six-year-old carpenter was admitted to the hospital because of epigastric distress of eight years' duration

The pain usually developed in the midafternoon and was promptly relieved by food or soda. On one occasion he vomited large quantities of bright blood.

Physical examination revealed a well developed man, with a blood pressure of 130 systolic, 80 diastolic. There was moderate exophthalmos and slight lidlag. The skin was slightly dry and cool. Examination of the chest and abdomen was negative. Urine, blood and stool examinations, including guaiac tests, were negative. Gastric analysis revealed 33 units of free hydrochloric acid. The serum cholesterol was 153 mg per 100 cc. A gastrointestinal series showed a small ulcer crater on the lesser curvature of the stomach just above the angulus. Basal metabolic rates on six occasions ranged from -30 to -40 per cent. Electrocardiograms showed bradycardia and low T waves. Three weeks of medical management brought symptomatic relief but produced little change roentgenologically in the gastric ulcer. He was discharged to the Out-Patient Department on a bland diet and alkali therapy.

Second admission (five years later) In the interim the epigastric distress was well controlled, and the patient failed to return to the Out-Patient Department. He had continued the discharge medication of 0.1 gm of desiccated thyroid and followed the diet rather faithfully. Nine months before this admission he gradually developed crampy, midepigastric pain about one hour before meals, which was not relieved by food or alkali.

Physical examination was essentially unchanged. The blood cholesterol was 417 mg per 100 cc. Basal metabolic rates again ranged from -39 to -46 per cent, and the protein-bound iodine was 0.4 microgm per 100 cc. Two gastrointestinal series again demonstrated the small lesser-curvature ulcer. Barium enemas and skull films were normal. He

was placed on a six-meal bland diet and 0.2 gm of thyroid daily, with considerable improvement, and was again discharged.

Third admission (one year later) He was fairly comfortable for three or four months, but then he became plagued again by his epigastric pain. Three weeks before entry he abruptly developed a tender swelling of the thoracic spine, which persisted unchanged. The only changes on physical examination were midepigastric tenderness and a tender, smooth swelling over the tips of the sixth and seventh dorsal vertebrae. The urine was normal except for 4 or 5 white blood cells per high-power field in the sediment. The white-cell count was 8650, the hemoglobin was 14.5 gm. The cholesterol was 192 mg and the esters 146 mg per 100 cc, and the calcium and phosphorus were normal. A gastrointestinal series again demonstrated the ulcer, which was slightly smaller than before. There was osteoporosis of the spine and a compression fracture of the ninth dorsal vertebra. Examination of the lungs and intravenous pyelograms were not remarkable.

A subtotal gastrectomy, with removal of a benign ulcer, was done. The patient convalesced well until the seventh postoperative day, when he developed right-upper-quadrant pain following meals and worse at night. On the eleventh postoperative day he abruptly passed a thin, bright-red, bloody stool and another an hour later. The pain, which had been intermittent and crampy at onset, became sharp and steady. Abdominal examination was negative, as were plain films of the abdomen. The abdomen was re-explored, with entirely negative results. He again convalesced well without pain or bleeding until the seventh postoperative day, when the upper-quadrant distress returned and was again apparently closely related to food, coming on ten to twenty minutes after eating. This was associated with nausea, a sense of abdominal fullness and dyspnea. After several days this syndrome was expanded to include an urge to defecate, with passage of thin, loose stools immediately after the pain began. These symptoms became quite incapacitating, and the patient failed to eat and gain weight. A gastrointestinal series showed the stump of the stomach to fill well and empty readily, with no demonstrable lesion. A serum amylase was 60 units. The pain was only partially relieved by atropine and demerol, and he consistently refused to eat because of the pain. After almost two months in the hospital at his own request he was discharged on a six-meal bland diet, atropine and phenobarbital.

Final admission (six weeks later) His condition after discharge became increasingly poor. He practically refused to eat at all because of the epigastric distress, nausea and diarrhea, which invariably followed eating even the smallest amount of food. The pain came in waves, was accompanied

by loud gurglings and lasted about one hour. He became emaciated and developed dyspnea, dizziness, palpitations, sweating and flushing, which occurred erratically in time, lasted only a few minutes and was not necessarily associated with the other complaints. He also noted grossly bloody stools on several occasions.

Physical examination revealed a tired, weak and emaciated man. The skin was dry, inelastic and warm. The chest was clear. There were numerous extrasystoles. The abdomen was slightly distended, with moderate tenderness just to the right and below the umbilicus. Peristalsis was active with occasional high-pitched gurgles. Rectal examination showed tenderness on the right side, but no masses could be felt.

The pulse was 45, and the respirations 20. The blood pressure was 105 systolic, 55 diastolic.

The urine was cloudy, with a specific gravity of 1.018. Albumin and sugar tests were negative. The sediment was loaded with white blood cells but no red blood cells. The blood hemoglobin was 15.5 gm. The white-cell count was 6250, with 59 per cent neutrophils. The stool was light tan and guaiac negative. The amylase was 25 units, and the total protein 5.86 gm per 100 cc, with an albumin-globulin ratio of 1.5, the nonprotein nitrogen was 24 mg per 100 cc. The van den Bergh reaction was 0.4 mg per 100 cc direct and 0.7 mg indirect. The prothrombin time was 20 seconds (normal, 16 seconds), the cephalin flocculation test was + in twenty-four and ++ in forty-eight hours. The cholesterol was 176 mg per 100 cc. The basal metabolic rate was -40 per cent and remained at this level despite intravenous administration of thyroxin. A gastrointestinal series showed barium to enter the stump of the stomach and pass readily into the efferent loop. There was no evidence of obstruction or marginal ulceration.

Numerous diagnostic studies were instituted in attempts to elucidate further the nature of the disorder, but the patient's course was little affected by the procedures tried. The appearance time of indigo carmine was five and a half hours. A glucose tolerance test showed a fasting blood sugar of 96 mg per 100 cc, with a rise of 137 mg in half an hour. The levels at one, two, three, four and five hours were 126, 111, 78, 69, and 72 mg per 100 cc, respectively. A vitamin A tolerance curve showed a fasting level of 1.3 units per cubic centimeter, and there was no rise at all in the subsequent specimens. A right splanchnic block (sixth to twelfth dorsal segments) with procaine was done, which diminished somewhat the pain during the period of anesthesia but did not relieve the tenderness. A differential spinal block was attempted, and with loss of pinprick sensations to levels of the second dorsal segment he was able to drink milk without pain, but the sense of distention and fullness was not altered. He continued to starve himself because of the severe

symptoms initiated by ingestion of food, and his condition deteriorated rapidly.

An intensive program of tube and intravenous feedings was undertaken, but he tolerated the tube feedings poorly, and they were discontinued. An abdominal exploration and feeding jejunostomy was done. No abnormalities were made out at the time of exploration. Postoperatively he continued to have the same severe midepigastic pain and marked nausea and vomiting. On the fifth postoperative day he began to vomit blood, and serosanguineous material exuded from the jejunostomy wound. He developed abdominal distention and diffuse abdominal tenderness. The blood pressure dropped to 60 systolic, 40 diastolic, and there were practically no peripheral pulses. He remained in a shock-like state throughout the day despite supportive measures and died quietly late that night.

DIFFERENTIAL DIAGNOSIS

DR ARTHUR W ALLEN I would like to have someone tell me whether the cholesterol esters (146 mg per 100 cc) were within a normal range.

DR CHESTER M JONES That is about normal.

DR ALLEN Thank you.

What about the vitamin A?

DR PERRY J CULVER It is a slightly high level. This indicates absorption and rise after a dose of vitamin A.

DR ALLEN I would like to see the x-ray films. It is a long case and a very complicated one, and unless I can get some help here I am not going to be able to tell what was the matter with this man.

DR STANLEY M WYMAN I do not know how much of the original examination to show, Dr Allen. These first two gastrointestinal examinations demonstrated in essentially the same position a crater just above the angle, which by x-ray examination appears grossly benign. As you recall, the benign character was confirmed at the time of the subtotal gastrectomy. He has a calcified aorta, which is unusual for a man of this age.

DR ALLEN Are there any esophageal varices?

DR WYMAN No, but he does not have a large spleen. Without splenomegaly varices would be quite unusual.

This film demonstrates the calcified abdominal aorta a little better, which is distinctly premature for a man of this age. The film of the thoracic spine, taken because of the swelling over the sixth spinous process, shows a compression fracture of the ninth thoracic body. The bones are quite osteoporotic for a man of forty-six, and one can see the dense calcification of the aortic arch — again, an unusual finding.

The first films of the stomach and upper gastrointestinal tract taken postoperatively show the stoma to be of good width. There is diffuse thickening of the gastric folds, but I cannot identify any evidence of ulcer at the stoma or other evidence of localized disease.

DR ALLEN Is there active peristalsis?

DR WYMAN Just a little overfilling of proximal small bowel because the barium ran through to the jejunum so rapidly

DR ALLEN Is this the afferent loop?

DR WYMAN It must be This shows a fairly normal transport of barium at the time of the examination, the barium reaching the ileum in about three hours The most striking thing, to my mind from these films, is the presumptive evidence of premature senility in a man of forty-six The osteoporosis of his bones, the arteriosclerosis and his chest all make him look considerably older than the age of forty-six or even fifty This film shows a slight increase in the anteroposterior diameter of the chest and degenerative changes in the thoracic spine with moderate osteoporosis, and the heart itself is not remarkable except that the aorta is calcified

DR ALLEN This is a very complex problem, and this man was prematurely old as demonstrated by the advanced arteriosclerosis and so forth Also there was an extraordinary persistence of a very low metabolic rate, even in spite of thyroid therapy That is very unusual I do not know how to explain it At one time the pulse was recorded at 45 His story gives me the impression of a hibernating animal, with his ability to subsist on a small amount of nourishment for an unusually long period in a situation that probably would have produced a fatal outcome much more quickly in the normal person There are many things about this that I do not understand I am not sure what other conditions could produce such a persistently low metabolic rate I am inclined to think that it was correctly recorded Obviously, the examiners were quite interested in the low metabolic rate, and the protein-bound iodine was, according to Dr Cope's information, which he was kind enough to give me, quite low and consistent with the low metabolic rate at that time

The long duration of the ulcer symptoms is a pretty good indication that he had a benign lesion rather than a malignant one He did very well with this ulcer, though it apparently never healed The change in the type of pain, which had previously responded to food and alkalis, suggests that perhaps something else was developing—something that also caused epigastric distress, but no longer of a type relieved by food and alkali It might be fair to assume that perhaps this new development was not related to the lesser-curvature ulcer

I do not know why the skull films were done, but they bring to mind the possibility of some cerebral lesion such as that described first by Dr Harvey Cushing¹—the association of lesions in the midbrain with ulcerations in the duodenum and in the stomach I do not believe that is a very likely possibility here, but it came to mind when I read this report

The osteoporosis is interesting, and taken with the spontaneous fracture of the ninth dorsal vertebra, makes me wonder whether it was simply dietary or whether there was some basic underlying metabolic disturbance that is not clear to me I do not know what the explanation would be This one instance of high recording of blood cholesterol, I think, might be a typographical error It is listed at 417 mg per 100 cc while every other one (and many others were done) was in a normal range

DR JACOB LERMAN It was before treatment

DR ALLEN That is the only time, before treatment, that we get any such level

The operation performed, I suppose, was a subtotal gastrectomy, with doubtless removal of the distal half or two thirds of the stomach, including the ulcer on the lesser curvature There is nothing unusual about that It was undoubtedly assumed that the bleeding experienced previously originated from the ulcer Then when he bled on the eleventh postoperative day the surgeons were disturbed because they wondered if it had anything to do with their suture line or whether they had overlooked some other lesion Of course, it is possible for a man to have an ulcer in the stomach and duodenum as well, and the ulcer in the duodenum might be far enough down so that the duodenal stump can be turned in without too much awareness of the situation on the part of the surgeon

The change in the character of the pain nine months before he came in the second time makes me believe that he did have something besides this ulcer of the lesser curvature The fact that he bled after resection, as late as the eleventh day, makes me believe that he bled, not from the suture line, in which case bleeding should have taken place about the seventh day or earlier, but from a lesion, whatever it was, that produced a change in symptoms and may very well have been related to the final outcome The fact that he was re-explored and nothing found wrong with the anastomotic site and no cause for the pain determined makes me wonder if this man had a lesion that could not be found within the abdomen by ordinary methods Could he have had a hidden lesion in that portion of the duodenum that cannot be seen readily without opening the mesentery over it, or could the bleeding have come from above?

The symptoms described here suggesting the dumping syndrome are interesting, but I am not of the opinion that this man could have had such a severe course, with the outcome as it was, on the basis of a dumping syndrome alone In some gastrectomized patients, the percentage is low, there is too rapid emptying of the stomach segment into the jejunum, with the symptoms described here—discomfort, usually called distress in the epigastrium, nausea and sweating that last for variable periods of time and usually go away about thirty minutes after the ingestion of food, particularly

if the patient lies down. The postoperative symptoms in this man were more severe than that. They were so severe that he did not dare take any food at all, because it initiated a gastrointestinal reflex, which was very marked, giving a five-and-a-half-hour time from the ingestion of carmine to the discharge of the dye from the rectum. That is a very rapid intestinal rate. Doubtless it is on that basis that the various tests were done on the parasympathetics and with spinal anesthesia.

A feature about this case that is disturbing and that I cannot understand is why this man had tenderness in the right lower quadrant. I cannot see why he should have right-lower-quadrant tenderness just on the basis of his rapid intestinal rate. It is conceivable, I suppose, that he did have a lesion in the cecum, but all the examinations with barium enema prior to operation failed to reveal any difficulty in the right colon.

The whole situation is further confused by the fact that, if I am interpreting this correctly, this man died of hemorrhage. It is very unusual to die of hemorrhage these days. There is usually enough blood around and it keeps going in and usually death can be staved off for an incredible length of time by that means. This man on his final day, being in a poor nutritional state, began to bleed and serosanguineous material came from the jejunostomy tube. He developed abdominal distention, with diffuse abdominal tenderness. It does not state whether he still had peristalsis. One might like to know that because, even in a man as sick as this, if we assume that all he did was to bleed to death, I think he still would have had peristalsis. If he had peritonitis, however, he would not have peristalsis. The fact that the man vomited blood and blood came from the jejunostomy tube probably rules out a source of hemorrhage lower than the high jejunum — that is, we must look for something from the esophagus, from the stomach, from the duodenum or from the first portion of the jejunum.

I wonder whether that is a fair deduction — whether or not he had something else. I am not prepared to say where the bleeding came from. We have these various sources of bleeding that we know about, — the esophagus, usually esophageal varices, and lesions in the stomach of all kinds, — but it is hard to believe that he could have had leiomyoma or cancer of the stomach or ulcer of the stomach that would not have been palpated at the last exploration. He could have had gastritis, I suppose. People have bled to death from gastritis alone. We have at least 2 cases in this hospital in which that has occurred. He could, I suppose, have had duodenal ulcer far down that was never felt and never demonstrated, from which he could have bled. He could have had a diverticulum of the duodenum, which was not picked up on x-ray examination and not seen at exploration. He could have had in that

duodenum gastric mucosa from which he could have bled. An ulcer could also have perforated finally into the peritoneal cavity, resulting in peritonitis.

DR TRACY B MALLORY: There is a note that in the final three hours peristalsis was minimal and sluggish.

DR ALLEN: Still present?

DR MALLORY: Apparently.

DR ALLEN: That would make it necessary for me to believe that this man bled to death from whatever lesions he had. I do not think we should forget the pancreas. He had had at one time slight elevation of the serum amylase. I doubt if pancreatitis would have lasted as long as this. The necrotizing type of pancreatitis causes death in the neighborhood of forty days, and erosion of the splenic vessels sometimes occurs with perforation into the colon or stomach, resulting in death by that route. It could, I suppose, have eroded into the duodenum or the jejunum, and the blood might have come from some such source. I doubt that we have enough evidence to back up erosion of the splenic vessels from pancreatitis.

Now, of course, I do not know how far general systemic disorders could have played a role in this case. It might be something that I have never heard of. At any rate, I must get through because I know a lot of you want to discuss it. This man had a gastric ulcer. We assume that he had hypothyroidism and marked arteriosclerosis, and he had a compression fracture of the ninth dorsal vertebra on the basis of osteoporosis and extreme malnutrition. Of all the things I can think of that satisfy me as to the final cause of death and the source of all his bleeding, a lesion in the third portion of the duodenum, which I am going to assume was probably a diverticulum, is the most probable.

DR MALLORY: This patient puzzled everyone in the hospital as much as he has Dr Allen. Almost everyone saw him and made a note at one time or other.

DR COPE: Have you anything to say?

DR OLIVER COPE: No one thought of Dr Allen's diagnosis. We should have considered it, practically everything else was considered. The Pathology Department did one kindness to Dr Allen. They left out some of the data that attracted attention way out in left field. In addition to hypothyroidism, the question was brought up as to whether he might have hyperparathyroidism. Dr Allen referred wisely to metabolic disturbances that might have given rise to the ulcer. We debated this back and forth, for there was a suggestion that he had hyperparathyroidism and coincidental ulceration in the upper intestinal tract. It was a good thought, but no one could make the diagnosis.

No one could understand why he had the pain, and I think it was fair to summarize the clinical opinions as follows: there was a suggestion of hyper-

parathyroidism, which was excluded because the evidence (I will not go into the data in detail) was equivocal, perhaps because the patient did not respond to thyroid. Dr Lerman will talk about the response to thyroid in a moment.

The neurosurgeons could not explain why he had pain. They thought that the only way to prevent pain was to go to the highest center—in other words, to do a lobotomy. The lobotomy would also have helped in the management, for the patient was suspicious and extremely difficult to handle. The Medical Service did an extraordinary job in keeping him alive. He required an enormous amount of care for four months throughout which he was in an extreme state of malnutrition. Finally, another point of view, which was the point of view adopted, was to re-explore the abdomen as a final measure on a chance that some lesion had been overlooked—the type of lesion Dr Allen referred to. Such an exploration was recognized to carry a high risk in a patient in such a condition and particularly since no one had any firm idea of what might be wrong. Exploration was carried out by Dr Welch.

DR LERMAN: I think there is no doubt about the diagnosis of myxedema. On the first admission the diagnosis was suggestive. When he came back the second time it was very obvious. Of theoretical interest is the possible etiology. He did have signs of residual exophthalmic goiter. The question arose whether it could be a rare type of hyperthyroidism that had burned out, with resulting myxedema. He responded to a special preparation, which we were using, called tetrabromthyronine. The statement is made that he did not respond to thyroxin. That is not true. The response was poor, but he did respond at one time to a dose of 1 mg of thyroxin for ten days when the basal metabolic rate went from -40 to -25 per cent, which is a poor result. The explanation for the response was that he was in such a poor nutritional state that he could not get up enough steam to make a response. It is interesting to speculate on the relation between prolonged myxedema and arteriosclerosis. It seems reasonable to expect that the hypercholesterolemia of myxedema will lead to extensive atherosclerosis in large and small vessels.

DR JONES: When I saw him several times at the request of the surgeons, it seemed to me justifiable to explore again, even in the absence of any positive findings, because of the intensity of the pain. It was directly connected with food. It was repeated over and over again, I am sure it was not a dumping syndrome. The pain was too severe for that. The main thing was that he did have a real intra-abdominal disease. We did not think he had an ulcer, as a matter of fact—at least, I thought he did not. I thought it was possible that he had a kinking with some obstruction by which pain was produced by peristalsis from time to time after

intake of food, and we decided that the only way to help was to go in and explore again, trying to find a lesion that might be treated.

DR CLAUDE E. WELCH: His outstanding symptom was pain. We thought that cancer of the pancreas would be the most likely diagnosis, but we really expected to find nothing. We found nothing.

DR ALLEN: I would like to add one thing. I did not mention the possibility of an anastomotic ulcer because of final bleeding. It is extremely unusual if it ever occurs following a gastrectomy for a gastric ulcer.

CLINICAL DIAGNOSES

Abdominal pain of unknown etiology
Myxedema
Arteriosclerosis

DR ALLEN'S DIAGNOSES

Gastric ulcer, postoperative
Osteoporosis, with compression fracture of ninth dorsal vertebra
Arteriosclerosis
Hypothyroidism
Duodenal diverticulum

ANATOMICAL DIAGNOSES

Atrophy of thyroid gland, with myxedema
Arteriosclerosis, severe, of aorta and mesenteric vessels
Congenital anomaly of mesenteric arteries, hypoplasia of celiac axis and hypertrophy of superior mesenteric
Thrombotic occlusion, old, of celiac axis
Thrombotic occlusion, fresh, of superior mesenteric artery
Incipient gangrene of small intestine
Osteoporosis
Slight hyperplasia of parathyroid glands

PATHOLOGICAL DISCUSSION

DR MALLORY: At autopsy in this case, the lesion found was in the mesenteric vessels. He had what I am quite sure was an anomaly to start with. The celiac axis was very small, and the superior mesenteric artery very large. The inferior mesenteric was also small, but I would assume the celiac axis was half normal diameter and the superior mesenteric was twice normal diameter. The celiac axis was almost completely occluded by an old, organized thrombus, and a large anastomotic vessel was found connecting the superior mesenteric and pancreaticoduodenal arteries. The stomach and spleen must have been nourished from the superior mesenteric artery through various anastomoses. The terminal episode was an acute thrombosis of the superior mesenteric, which had cut off the blood supply of almost the entire intestinal tract between

the esophagus and the colon. It was partially infarcted. At autopsy we found no intrinsic lesion in the remainder of the stomach or elsewhere in the intestinal tract. So I think the sclerotic changes in the mesenteric vessels probably were the cause of the persistent pain. At least, we have no other explanation for it.

A few other findings at autopsy were interesting. The thyroid gland was almost completely atrophic, and in numerous sections we were able to find only four or five recognizable thyroid acini. The rest was reduced to fibrous tissue. The parathyroid glands seemed slightly hyperplastic. Certainly, the proportion of parenchyma to fat cells was increased, but because of the emaciation the ratio may have been disturbed by loss of fat cells. The pituitary body was normal.

DR JONES: This could be explained, it seems to me, on the theory that the patient had a minimal local blood supply, and the minute one increased the demand for blood by putting in food, the local blood supply was inadequate and it caused "anginal" pain.

DR MALLORY: The abdominal aorta was extraordinarily sclerotic, as shown in the x-ray films, and the atheromatous plaques markedly narrowed the mouths of all these arteries. There was also sclerotic involvement of the vessels themselves.

DR COPE: May I ask Dr Allen to comment finally? Our impression, in retrospect, is that the patient had abdominal angina. I have never seen this before. Is that a reasonable diagnosis to entertain here?

DR ALLEN: I think it is. I think that is all right. It has been reported. Cushman and Kilgore,² of San Francisco, reported a case. Dr Jones's explanation is quite reasonable. I think a man who has angina pectoris gets an attack with an increased demand on the heart. Therefore, it seems to be a very reasonable deduction that increased demand on the stomach caused this epigastric pain. But it is a little hard for me to understand why he bled so much from the stomach — a little difficult for me to understand why, in other words, an organ that had insufficient blood supply should not be less likely to bleed than the normal.

DR COPE: He bled after both operations.

DR ALLEN: And before.

DR MALLORY: I think it is important that the coronary vessels were in good shape. There were a few thrombosed plaques, but no significant narrowing. The possibility of cardiac angina with reference of pain to the abdomen is therefore improbable.

DR COPE: In summary, you think it is reasonable to make a diagnosis of prolonged myxedema and atherosclerosis with abdominal angina?

DR MALLORY: That is the best explanation I can give.

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CASE 35072

PRESENTATION OF CASE

A nineteen-year-old girl was admitted to the hospital because of severe headache and right orbital swelling.

She had been perfectly well until five days before admission, when she began to have intermittent pain behind both eyes and over the right side of the face and head. The pain became progressively more severe and three days before entry was constant and prevented sleep. At this time tearing of the right eye and dripping of a clear fluid from the right nostril developed. On the following day she developed photophobia in the right eye and vomited three times. Twenty-four hours before admission a short trial with ergotamine tartrate was unsuccessful, but it was thought that she improved following pyribenzamine. There was no fever. However, the pain increased, and that night the right eye began to swell.

Physical examination revealed a well developed and nourished girl who was very drowsy but capable of being aroused and of performing simple tests. The skin was hot. There was marked swelling about both eyes with chemosis, moderate proptosis and supraorbital tenderness, more pronounced on the right side. There was thought to be slight peripapillary edema of the retina. The pupils measured 3 mm in diameter and reacted briskly to light. The external movements of both eyes were "reduced in all directions." There was marked tenderness on the right side, and slight tenderness on the left in the preauricular region and over the right lower jaw. There was a small amount of purulent secretion (less than 1 cc) in each nostril. The middle and inferior turbinates were slightly injected bilaterally. The ears were normal. The neck was rigid, and Kernig's sign was positive. There was dullness over both lung bases posteriorly, breath sounds over the left base were coarse and high pitched on the right. There was tenderness in both upper quadrants of the abdomen and costo-vertebral-angle regions.

The temperature was 103°F, the pulse 80, and the respirations 32.

The urine was normal. The blood hemoglobin was 11.5 gm, the white-cell count was 16,500, with 86 per cent neutrophils. A blood culture was later reported to have grown *Staphylococcus aureus*. A lumbar puncture revealed cloudy spinal fluid under a pressure equivalent to 270 mm of water. Jugular compression on the right produced no change in pressure, on the left it resulted in a good rise. The

cell count was 7000, with 93 per cent neutrophils. A culture was negative.

The patient became more stuporous, and the temperature rose to 104°F. Roentgenograms of the skull and sinuses were normal. She was immediately started on penicillin, streptomycin and intravenous heparin. On the second hospital day the temperature was still elevated, the prothrombin time was 25 seconds (normal, 16 seconds), following which dicumarol therapy was begun. It was noted that the left eye had become as swollen as the right. A second lumbar puncture produced a cloudy, yellow-tinged spinal fluid containing only 481 white cells per cubic millimeter. On the fourth hospital day the prothrombin time was in the neighborhood of 50 seconds (normal, 18 seconds). On the same day the patient had a seizure consisting of clonic movements of the left side of the body, beginning in the face and extending downward, lasting about a minute. Several more seizures occurred but ceased after she had been given dilantin and phenobarbital. Later that day she was semicomatose and found to have a left hemiparesis and hemianopsia. The white-cell count had fallen to 4700, with 80 per cent neutrophils, sulfadiazine administration was stopped. On the next day, however, these last findings had cleared considerably, and although the temperature still fluctuated between 101° and 102°F, she seemed much improved. There had been a progressive reduction in the number of cells in the spinal fluid. The periorbital swelling was considerably reduced, and she was able to open her eyes and look around. On the eighth hospital day, after continued improvement, she complained of chest pain, first on the left and later on the right, accentuated by deep inspiration.

On the following day the white-cell count had risen to 12,300. There was no cough or hemoptysis, and examination of the legs was negative. A roentgenogram of the chest disclosed three small areas of increased density overlying the posterolateral portions of the fifth and seventh ribs on the right side and the ninth rib on the left. Heparin was again started. Twenty-four hours later she appeared acutely ill, pale and moaning. The temperature was 101°F, the pulse 90, and the respirations 25. There were tenderness over the right temple, and tenderness, marked redness and edema of the right eyelid. The right eye was proptosed, and the conjunctiva showed severe chemosis with slight, pink tearing. There was moderate nuchal rigidity, and a positive Kernig's sign, more marked on the left. A lumbar puncture revealed a spinal-fluid pressure equivalent to 180 mm of water and containing 28 neutrophils per cubic millimeter and a negative smear and culture. On the following day the fundi showed retinal edema, the disk margins were blurred and indistinct, and there was a suggestion of papilledema. The prothrombin time was 24 seconds (normal, 16 seconds).

After another brief period of improvement the patient began to complain of severe pain in the eyes and right ear. She was drowsy most of the time. On the next day she complained of the pain almost constantly and was obviously much weaker. Later in the same day she tried to vomit but could only retch, shortly after which she became unresponsive. The left corneal reflex was absent. There was ankle clonus, moderate on the right and slight on the left, and a positive Babinski on the right. She remained unresponsive and died several hours later, on the thirteenth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. AUGUSTUS S. ROSE. From the history, physical findings and course of this patient we have little question regarding diagnosis. It is obvious that the patient had an infectious process involving the dural sinuses, and in view of the positive blood culture for *Staph aureus* and the early response to therapy we must assume that the infecting organism was *Staph aureus*. There are a number of questions, somewhat unanswered, that require consideration. In the first place, we are told that she was well until five days before admission, eighteen days before death. This is a very rapid termination, particularly in view of the excellent therapy on admission to the hospital, which included sulfadiazine, streptomycin and penicillin. If *Staph aureus* was the only organism, these therapeutic agents should have done—or we would have hoped that they would have done—a better job in arresting the infectious process. The question that bothers me most of all is the source of the infection. The patient was apparently entirely well, no mention being made of a pimple or other local infection on the face or within the nose. The only leads we have are the early symptoms and the finding of pus in the nose. Back in the days before chemotherapy the development of cavernous-sinus thrombosis, which I believe this patient had, was sufficient evidence for immediate consideration of ethmoid sinusitis in the absence of infection on the face. Despite a negative x-ray examination, an acute infection of the ethmoid sinuses may have been the original source of infection. The first symptom recorded was pain behind both eyes, followed very quickly by pain in the face, on one side, and some tenderness and then swelling. Presumably because of the absence of fever, her physician thought of migraine, for which he prescribed ergotamine, and also of a histamine reaction of some sort because of the pyribenzamine. With the entire case before us, the pain behind the eyes makes me think of ethmoiditis. But probably at this time the patient had already begun to develop thrombosis of the cavernous sinus, chiefly on the right. The thrombus was probably infected from the beginning despite the absence of fever. With rapid succession there was swelling of the right eye,

followed in a day by swelling about the other eye. The thrombosis or thrombophlebitis of the cavernous sinus on the right spread via the circular sinus to involve the cavernous sinus on the left. We then have the information of a lumbar puncture done on admission, which showed no rise in spinal-fluid pressure on compression of the right jugular vein, giving evidence that the right lateral sinus had become occluded by the thromboinfectious process. The patient was drowsy, showing considerable involvement and disturbance in function of the brain, and the spinal-fluid pressure was elevated, indicating that venous return from the brain was interfered with. The cell count in the spinal fluid of 7000, predominantly polymorphonuclears, does not of necessity mean a bacterial infection of the surface of the subarachnoid space. But it does point to infection nearby. The two negative cultures of spinal fluid and the absence of bacteria support the concept.

The patient complained of pain in the chest. The House Service evidently thought in terms of emboli because they give us a negative report on the veins of lower extremities, and we also are told that she did not have hemoptysis. X-ray examination, however, showed a shadow in the lung consistent with pulmonary embolus, and I expect that it was an infected embolus without abscess formation. Eighteen days following the onset of the illness is too short for an abscess to form in the lung or in the brain.

The patient was drowsy and had a convulsive seizure on the left side, the opposite side from the occlusion of the lateral sinus. I would reason that the thromboinfective process had extended backward through the sinuses of the dura into the veins of the brain itself and had caused changes within the brain, which may well have been the beginning of an abscess. If she had survived, it is possible that she might have had a circumscribed abscess within the brain, but I doubt if autopsy revealed definite abscess formation.

One other question is, Why did not adequate treatment, which she presumably had, stop the infection? I have to leave that unanswered but assume that this patient's resistance was low, that the virulence of the organism was great and that, by the time treatment was started, infection had already spread not only into the blood stream and cavernous sinuses but also beyond and was an overwhelming infection.

I then summarize by saying that I believe the patient had a primary infection in the ethmoid sinuses from which there developed a thrombophlebitis involving the right cavernous sinus, the right lateral sinus, the left cavernous sinus, the veins of the brain, septicemia, pulmonary infarct and possibly a beginning abscess on the right side of the brain.

DR TRACY B MALLORY Are there any interesting x-ray films?

DR STANLEY M WYMAN I doubt if they are contributory.

DR MALLORY Are there any questions or comments?

DR JAMES B AYER The test for lateral-sinus thrombosis on the right is more accurate than that on the left, so I think Dr Rose's reasoning is probably correct.

CLINICAL DIAGNOSES

Cavernous-sinus thrombosis
Meningitis
Sinusitis
Pulmonary emboli

DR ROSE'S DIAGNOSES

Ethmoiditis
Thrombophlebitis, cavernous sinuses and right lateral sinus
Thrombophlebitis of cerebral veins, with cerebral necrosis
Septicemia
Pulmonary emboli

ANATOMICAL DIAGNOSES

Ethmoiditis and sphenoiditis
Thrombophlebitis of cavernous sinuses and tributary cerebral veins
Venous cerebral infarction
Massive cerebral hemorrhage
Subdural hemorrhage
Meningitis, healed

PATHOLOGICAL DISCUSSION

DR CHARLES S KUBIK The posterior ethmoid cells and sphenoid sinus contained not thick pus but brownish-orange, thick fluid. That presumably was the source of infection along veins of the air sinuses, which empty into the cavernous sinuses. The venous sinuses, with the exception of the cavernous sinuses, were normal. The cavernous sinuses were removed intact with the central portion of the sphenoid bone, sphenoid sinus and posterior ethmoid cells, and on microscopical sections were found to contain purulent exudate and organized thrombi on both sides. There was also infection in the circular sinus, which passes around the pituitary gland and connects the two cavernous sinuses. It is through the circular sinus that infection extends from one side to the other. In the right posterior parietal and temporal regions there was a subdural clot of blood, 0.2 or 0.3 cm in thickness and 3 to 4 cm in diameter. There was blood, apparently fresh, in the subarachnoid space, extending medially to the base of the brain, and a large cerebral hemorrhage, measuring between 4 and 5 cm in diameter, in the right posterior parietal region.

On microscopical examination there was a fair amount of organization of the subdural hemorrhage, indicating that it must have occurred at least a number of days before death. The cerebral and subarachnoid hemorrhage appeared to be recent. In the same region there were thrombosis of cerebral veins that drained into the cavernous sinus and hemorrhagic foci of necrosis of the brain such as occur with arterial and sometimes with venous occlusion. I believe that thrombosis unquestionably extended in retrograde direction from the cavernous sinus to tributary cerebral veins, as suggested by Dr. Rose, and resulted in venous infarction of the brain. Infarcts of the brain, following arterial occlusion, usually are pale with hemorrhagic areas here and there, resulting from innumerable, small, diffuse extravasations and capillary hemorrhages. Venous infarcts are much more likely to be hemorrhagic. Massive hemorrhages are unusual. In this case I believe that the terminal event was a massive hemorrhage, which began as the usual type of hemorrhagic venous infarction. Microscopical examination indicates, I believe, how the large hemorrhage developed. There were some foci of infarction with a few, punctate hemorrhages and other similar foci, with a small, massive hemorrhage in the center. It seems likely that the large hemorrhage began in the same way, or possibly as a number of such small lesions.

There was no grossly visible pus in the orbital tissues — only some punctate, hemorrhagic foci. Microscopical examination of the orbital tissues revealed the ophthalmic veins filled with bland thrombi and surrounded by partly organized hemorrhages and, on the right side, a small, partly walled-off abscess. The optic and oculomotor nerves looked normal.

The spinal subarachnoid spaces contained a few lymphocytes, plasma cells and large mononuclear cells, and there was possibly slight arachnoid

fibrosis — actually surprisingly little reaction, even for recently healed meningitis. The spinal cord itself and the spinal nerves were normal.

There had been indications of considerable clinical improvement for a time after treatment was begun. The mental status improved, proptosis diminished, ocular movements returned, and cells in the spinal fluid dropped from 7000 to 28 per cubic millimeter. The pathological findings also suggest that the natural course of the disease had been greatly modified. Before sulfonamides and antibiotics were available, thrombophlebitis of the cavernous sinus was invariably fatal, at least when it occurred in the severe form observed in this case. At post-mortem examination the cavernous sinuses were distended with pus, and the orbital tissues were honey-combed with abscesses. In this case it is quite possible that recovery would have taken place but for the hemorrhage.

DR. ROSE: Do you believe that the heparin and dicumarol aided the process of intercerebral bleeding?

DR. KUBIK: I think that is quite possible. We have suspected it in cases of subacute bacterial endocarditis, treated with anticoagulants, in which massive cerebral hemorrhage of the brain occurred, apparently in a region of embolic infarction.

DR. JOHN B. STANBURY: Were there any thrombi in the vessels of the neck?

DR. MALLORY: None were found outside the cranial cavity. In the lungs there were multiple, irregular areas of hemorrhage having the appearance of very fresh, slightly atypical infarcts, some of which showed beginning softening in their centers, suggesting that they were septic in character, not as yet broken down into frank abscesses. They were too recent for that.

A PHYSICIAN: How much penicillin was she given?

DR. W. H. TIMBERLAKE: She received amounts varying from 100,000 to 500,000 units every three hours.

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EX LIBRIS

Two of the important factors that distinguish man from less elevated animals are the ability to reason and the capacity for speech. A refinement that has enabled each generation of mankind to profit most fully from the experiences of its predecessors has been the recording of ideas and the preservation of these records, whether carved in stone or scratched in tablets of clay, whether traced on papyrus or written in manuscripts or impressed upon the printed page.

Only by consulting its records has man been able to build adequately upon the experiences of the past, of greater importance to his progress than the invention of the wheel has been his establishment of the library, which contributes to his cultural and spiritual as well as to his technical advance.

Some of the brightest chapters in the story of mankind have been illuminated by the development and preservation of literature. Some of the darkest pages in history have been punctuated by the destruction of libraries and the burning of books, from the conflagration at ancient Alexandria to more recent attempts at the destruction of modern culture.

The library as an institution has been one of man's sacred heritages. This applied to the first Sumerian tablet that was laid aside to tell its story four thousand years later, it applies to the most recent text that has been placed on file. This institution is an urgent public charge, from the Library of Congress, supported by an assessment on all the taxpayers, to the smallest village library in existence. And not the least important of these repositories of learning is the Boston Medical Library, which has happily become, as emphasized recently in these pages,* one of the solemn responsibilities of the Massachusetts Medical Society.

In making his contribution to the perpetuation of a library and the continuance of its services, the responsible citizen, whether layman or physician, by no means has in mind what particular benefit he as an individual will derive from it. He can no more calculate the returns on his investment in terms of personal advantage than he can the returns from his contributions to a hospital, the Red Cross, the Salvation Army, the community chest or his church.

The Massachusetts Medical Society has voted an increase in its annual assessment to \$25. Of this sum, \$5.00 from each fellow was allocated to the use of the Boston Medical Library, and has proved to be a most welcome transfusion for this invaluable institution. The discharge of this barest obligation, however, is not enough. There must be in addition an increasing number of thoughtful and responsible physicians willing and eager to pay an additional \$15.00 for fellowship in the Library — not for themselves but to help in preserving the very foundations of their profession.

Nor is this enough. The immediate future of the Library requires the expenditure of \$75,000 for the erection of new stacks, an expansion that is neces-

*Editorial Budget for 1949 *New Eng J Med* 239:155, 1949

sary in order that the institution may continue to rank among the foremost medical libraries of the world. This cannot be done from current income, even if augmented by the accession of new fellows. It must be accomplished as the result of an intellectual renaissance among the physicians of New England, expressed in terms of a material contribution that some modern form of alchemy can convert into the metal of which such equipment is constructed.

MEETING OF THE COUNCIL

THE midwinter meeting of the Council of the Massachusetts Medical Society, held on February 2, would have been of particular significance because of one fact alone. That was the unanimous approval of the action of the Executive Committee in authorizing the Secretary to proceed, as an agent of the American Medical Association, in collecting the assessment that the Association has levied on its members.

Of further significance was the Secretary's report that within two weeks of the mailing of the notice more than 1500 checks have been received from over a quarter of the Society's fellowship, some of the contributions being for sums in excess of that called for. Remarkably few direct refusals to contribute have been received, some of the fellows of the Society have expressed their desire to withhold their contributions until assurance can be given that the American Medical Association will use the fund wisely and constructively.

Under new business the spokesmen for a group of sincere and thoughtful younger fellows of the Society suggested certain constructive proposals that the Society might endorse and strongly recommend to the Association for its adoption. These proposals expressed a belief that the health of the people will be best served by medical care free of Government administration and control, and called attention to the profligate waste and duplication in health programs operated by the Government, as reported by the Hoover Commission. They indicated the belief of their proponents that the manner of expression of policy on the part of the American Medical Association has served to diminish public confidence in that body, and that its

policy should be one of more active and enthusiastic support of constructive proposals for more equitable distribution of medical care. They further suggested endorsement by the Council of the principles for the distribution of medical care that were agreed upon by the Section on Medical Care of the National Health Assembly held in Washington in May, 1948.

These proposals were referred to a joint committee of the Committee on Public Relations and the Committee on Medical Economics.

The reports of the various committees were accepted and their recommendations in general were adopted, the recommendations of the Advisory Subcommittee on Malpractice Insurance regarding listeners at malpractice suits were, however, rejected.

AUREOMYCIN — ANOTHER EFFECTIVE ANTIBIOTIC

THE antibiotics that have proved most active or most promising for clinical use have come either from molds, like penicillin, from spore-forming bacilli, like gramicidin (tyrothricin), subtilin and bacitracin, or from actinomycetes of the genus *Streptomyces*. A concentration of interest in strains of the last genus was stimulated, of course, by the high activity and effectiveness of streptomycin. Another of the recent antibiotics derived from a species of *Streptomyces* was chloromycetin. Some of the unusual properties of this antibiotic — namely, its high degree of effectiveness against rickettsias and against certain of the large viruses as well as the in vitro susceptibility of both gram-negative and gram-positive organisms to that agent — have been referred to in these columns.¹

A new antibiotic, aureomycin, that is derived from a species of soil organism, which has been named *Streptomyces aureofaciens*, has now been shown, on the basis of laboratory evidence and clinical trials, to give promise of being a useful addition in this field. The early reports presented at the New York Academy of Sciences last July² and additional papers that have already appeared^{3, 4} have indicated that aureomycin, like chloromycetin, should prove most useful against infections with all the known rickettsias and with the viruses of the

mphogranuloma-venereum-psittacosis group. In addition, aureomycin has been shown to be of considerable, though more limited, therapeutic value in many infections with gram-positive and gram-negative bacteria. Like chloromycetin it has the advantage of being effective when used by mouth and is relatively nontoxic.

The exact field of usefulness, the toxicity and the limitations of this new antibiotic, however, are still to be worked out.

The paper by Finland, Collins and Wells in the present issue of the *Journal* and similar observations by other workers^{13, 14} suggest that aureomycin may also be highly effective in the treatment of cases of primary atypical pneumonia, although the authors are quite cautious in the interpretation of their results. These findings, however, should stimulate further attempts to isolate and define the etiologic agent in this disease, which has become increasingly prominent as the seriousness of the bacterial pneumonias has been reduced by the use of the available chemotherapeutic and antibiotic agents.

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—WHAT THY RIGHT HAND DOETH

SOMETHING more than a generation ago universal custom demanded that the American school child write with the right hand, or else. A small

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This later revelation of recent decades, while it disclosed the injustice that had been done to one group of embryonic citizens, set all to rights for the next. The pendulum that had reached the northernmost antipode of its excursion swung back upon its course and drove with equal vigor to the left. Since then it has been a foolhardy teacher indeed, or the most ignorant of parents, who would dare disturb the handedness with which heredity, chance, divine providence or a solemn design of inscrutable nature had endowed a child.

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The conclusion may be drawn that environmental pressure is highly important in determining ultimate handedness and that unless inherent preference for the left is particularly strong, an artificially imposed shift to the right may not be the crime against humanity that it has so recently been considered. Ambidexterity introduces the really confusing factor. It is ambidextrous persons who sometimes know not which way to turn and whose left hands really know not what their right hands do, less certain in their abilities than the companies that rallied to David who "were armed with bows, and could use both the right hand and the left in hurling stones and shooting arrows out of a bow."

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MASSACHUSETTS HEALTH CONFERENCE, INC

AN outstandingly progressive step toward the better distribution of medical care in Massachusetts was taken on November 28, 1948. On that date representatives of fifty or more "consumer" and "distribution" groups met together and organized the Massachusetts Health Conference, Inc.

First fruits of this organization consist of the Conference about to take place, on February 19 and 20, at the Hotel Statler, in Boston. Honorary chairman of the Conference is His Excellency, Governor Paul A. Dever, the chairman is Mr. Philip R. Mather, president of the National Health Conference. The president is Dr. John F. Conlin, director of medical information and education of the Massachusetts Medical Society, the vice-president is Mr. John J. Devlin, of the American Federation of Labor, and the secretary-treasurer is Mr. Louis T. Maloney, executive secretary of the Massachusetts Dental Society. The first Conference objective is "Means of Improving Health in Massachusetts during the Next Five Years."

It is a notable thing when members of diverse groups including both distributors and consumers sit down together to discuss their mutual problems, and a refreshing acknowledgment of the fact that most worthwhile objectives need to be viewed from various vantage points.

MASSACHUSETTS MEDICAL SOCIETY

TREASURER'S OFFICE

All members should be reminded that the proportion of the refund returned to each district society is based on the number of dues paid by March 1 in that district, and also that the names of members who have not paid their dues by March 1 are automatically removed from the mailing list of the *Journal* until such dues are paid. This year \$8000 is being returned to the district societies.

ELIOT HUBBARD, JR., *Treasurer*

BOSTON MEDICAL LIBRARY

Thanks to the loyal support of the members of the Massachusetts Medical Society the Boston Medical Library has been able to render greater service than ever before. During the past year 42,638 books and periodicals were made use of whereas the previous highest circulation had been

38,266 in any one year. Of considerable interest is the fact that over 9000 users of the Library were neither fellows, Society members nor members. This is the kind of service that should be rendered and rendered gladly. It represents the same type of service rendered by a free public library, which must be paid for out of taxes. The added income received from the Massachusetts Medical Society members enables the Library to furnish this service.

The personnel of the Library has been increased and 1000 more periodical volumes have been prepared and bound than during the previous year. The library has increased in size by over 2500 volumes and 4000 pamphlets. It is still far from its goal, but it is on its way.

The great need now is to obtain enough money to complete the stacks so that valuable volume will be more readily available. This will cost approximately \$75,000.

Next year the Boston Medical Library celebrates its seventy-fifth anniversary, and it is hoped that it may be celebrated by dedicating the new stacks. The members of the Massachusetts Medical Society can rightly take pride in their contribution to help support and carry on the work of this great and valuable library.

WALTER G. PHIPPEN, *President*

CORRESPONDENCE

COMMITTEE FOR THE NATION'S HEALTH

To the Editor: A bill has been introduced into the 81st Congress to develop a national health program. With the President strongly in its favor and the Congress composed as it is, there is a reasonable chance that such legislation will be enacted into law. It is important, therefore, that the medical profession and others to whom Congress will turn for advice be so informed on the subject that clear thinking will result. Unfortunately, appreciable misinformation regarding the subject has been broadcast throughout the country. A recent example is the inaugural address by Dr. William B. Rawls on assuming the presidency of the Medical Society of the County of New York. This address, which received publicity in the lay and medical press, contained many inaccurate statements and misleading innuendoes, and specifically mentioned me and the Committee for the Nation's Health, of which I have the honor to be chairman. I have corresponded with Dr. Rawls in the hope that he would be willing to correct these inaccuracies, but we have been unable to come to an agreement on the facts. We have left our correspondence with the understanding that I would present my point of view for the benefit of the physicians and laymen. Naturally, I prefer to present the subject through the medical press, and therefore, I hope you will be willing to publish this letter in the *Journal*, which is the medium in which I should like to have any communication from me published.

In his address Dr. Rawls says, "One of the major weaknesses of Compulsory Health Insurance is that it makes no provision whatsoever for the care of those people who are not able to pay their own medical expenses." In all the proposed legislation so far supported by the Committee for the Nation's Health the medically indigent — namely, those provided for in part by Government or charity — will cease to be indigent and under the plan become the private patients of their own physicians. Furthermore, provision is made under the plans so that local communities can insure the really indigent for whom they must accept responsibility.

The address presents as evidence for Dr. Rawls's point of view the study of the status of medical care in the United States by the Brookings Institute without pointing out that

two experts in the field have filed an unchallenged criticism of this report with the Sub-committee on Health of the Senate Committee on Labor and Public Welfare

The address says that compulsory health insurance will result in the socialization of medicine. At the present time we do not have compulsory health insurance, but we do have a great deal of socialized medicine as defined by General Paul R. Hawley, chief executive officer of the Blue Cross and Blue Shield Commission, who says, "Socialized medicine is medical care supported in whole or in large part by tax money and regulated by the government." Among good examples are the United States Public Health Service, the Veterans Administration, state universities and many tax-supported hospitals.

Dr Rawls calls attention to the statement of Bernard M Baruch, regarding the relation of doctors to Government "I oppose socialization here. It leads ultimately to the police state, degradation of the individual and lessened well-being." No mention was made that in the same speech Mr Baruch said, "Your organizations have been particularly active in pressing voluntary health insurance. But I would not be frank — nor friendly — if I did not add what you know. It is not good enough." Mr Baruch then went on in the same speech to propose compulsory health insurance. He declared "Nationally, the program might well be administered by a body of doctors and non-doctors to keep medical care as free from politics as possible." This program, he pointed out, "can be devised, adequately safeguarded, without involving what has been termed 'socialized medicine'."

Without specific reference the address stated that recent public-opinion polls have shown that compulsory health insurance is not the desire of the people. The following specific references on this subject are offered

A statement by the National Opinion Research Center, University of Denver, in 1944, that "85 per cent thought social security should include doctor and hospital care"

A 1946 poll by the California Medical Association showed that 50 per cent of California residents favor some Government medical program

A poll in 1946 in New York State under the direction of a Commission on Medical Care appointed by Governor Thomas E. Dewey showed that 84 per cent of New York State residents want health insurance

Although the address did not specifically say that everyone who is in favor of what is loosely called socialized medicine is a Communist, appreciable space was given to the innuendo that those supporting compulsory health insurance are dominated by Communism. A survey of the individuals and groups supporting the compulsory health insurance program should make clear to any fair-minded person the absurdity of this innuendo. President Harry S. Truman, Jonathan Daniels, Russell Davenport, William Green, Bishop Francis J. McConnell, Philip Murray, Bishop G. Bromley Oxnam, Mrs. Franklin D. Roosevelt, David Sarnoff, Gerard Swope, Dr. Thomas Addis, Barry Bingham, Dr. Ernst P. Boas, Morris Llewellyn Cooke, John J. Corson, Mrs. Gardner Cowles, Michael M. Davis, Albert W. Dent, Abe Fortas, Mary Dublin Keyserling, Carl C. Lang, Mrs. Albert D. Lasker, Dr. John V. Lawrence, Dorothy Norman, Emil Rieve, Anna M. Rosenberg, V. Henry Rothschild, Second, R. M. Walls, D.D.S., and Matthew Woll. The program is also supported by six United States Senators, four of whom are members of a church that is irreconcilably opposed to Communism. Seventeen national organizations with memberships totaling some 18,000,000 persons endorsed nation-wide compulsory health insurance last spring at the National Health Assembly.

The address of Dr. Rawls declared that the conclusions of the Congressional Sub-committee on Publicity and Propaganda, often spoken of as the Harness Committee, have never been seriously denied. This committee claims that federal employees spent public funds improperly in furthering the cause of compulsory health insurance. The address did not mention that these charges have been referred to the Attorney General of the United States, and that he has up to the present time not seen fit to act upon them, which at least suggests that the charges of the Harness Committee cannot be substantiated.

The Tokyo Mission was cited as another instance of an attempt of Government employees to promote socialized medicine, the following quotation of the Harness Com-

mittee's Report being held as an example "The real purpose of this Mission was to lay the groundwork for a system of socialized medicine in Japan and the scheme for such a Mission originated in the Division of Research and Statistics in the Social Security Board in Washington and nowhere else." Actually, it had been clearly demonstrated to this Senate Subcommittee that the Administration's health experts went to Japan at the explicit request of General MacArthur and his staff. In an official communication to Representative Harness, chairman of the committee that spread the false charge, MacArthur made clear that the request originated in his office, and that the purpose of the mission was to help reconstruct the national health insurance system, which had been instituted in that country by the Japanese in 1926.

The address said that Michael M. Davis, one of the principal founders and the most active member of the Committee for the Nation's Health was formerly an employee of the Social Security Administration. To correct this I call attention to the fact that Dr. Davis has never been a federal employee. Like many distinguished experts he has been asked by the Government to assist as a consultant from time to time. There is pay at \$25.00 per day for a consultant. A consultant, however, is not an employee.

The address called attention to the fact that the Committee for the Nation's Health is registered with the Government as paid lobbyists. This is correct. If the implication in the address is that such activity is improper, it is only fair to call attention to the fact that the American Medical Association maintains a registered lobbyist in Washington and that the National Physicians Committee, closely allied to and approved by the American Medical Association, is also so registered, and further that its annual expenditures are ten times that of the Committee for the Nation's Health.

The address quotes from a report of the Canadian Royal Commission about the German plan of "political medicine" since 1884 as follows "You will note the ever-expanding medical bureaucracy with its ever swelling tide of taxes and appropriations. After this process had been going on for fifty years, the whole arrangement was taken over lock, stock and barrel by Adolf Hitler, and the government's medical program was looked upon by many as one of the greatest props of the totalitarian state." Just what implication is meant from this quotation is not clear, but the address failed to mention that this same commission recommended Nation-wide Compulsory Health Insurance for Canada and that this recommendation was approved by the Canadian Medical Association. There are no obscure implications in these last two statements.

My hope is that the above corrections regarding fact and misleading innuendoes will permit members of a scientific profession to reach a decision about what type of national health program will be best.

CHANNING FROTHINGHAM, M.D.

101 Bay State Road
Boston 15

FAVORING THE ASSESSMENT

To the Editor: To those who object to the \$25 assessment that we may have medical freedom, the answer can be given that indirectly they are paying Mr. Ewing far more per capita to secure their enslavement.

The assessment is a small amount, and all should cheerfully contribute that much and more, if able, in order to maintain our medical standards as they are and not to have directives from Washington.

JUSTUS G. HANSON, M.D.

218 Elm Street
Northampton, Massachusetts

BOOK REVIEW

Handbook for the Medical Secretary. By Miriam Bredow. Second edition. 8°, cloth, 389 pp., with 36 illustrations. New York: McGraw-Hill Book Company, Incorporated, 1948. \$2.75.

This handbook, first published in 1943, has been revised, and the text brought up to date. A new section on secretarial duties in relation to veteran patients has been added to this edition. The whole field of office and patient management is covered, and there are special chapters on the preparation of manuscripts, the doctor and the law and the dental secretary.

The *World List of Scientific Periodicals*, which is not generally used to any great extent in the United States, is employed by the author instead of the abbreviations of the *Quarterly Cumulative Index Medicus* and the *Index Catalogue*, which are commonly used in this country. In the chapter on medical terminology there is a large vocabulary, comprising over 2000 medical terms, arranged by sixteen subjects. This list would have been more useful if all the terms had been arranged in one alphabet. The volume is well published. The work is intended as a student's textbook in teaching institutions, presenting courses for medical secretaries, office assistants and laboratory technicians. The book should prove useful also to all medical secretaries and should be in all medical libraries as a reference text.

NOTICES

NEW YORK STATE FELLOWSHIPS FOR TRAINING IN PUBLIC HEALTH

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GASTRIC ULCER*

A Study of the Massachusetts General Hospital Cases During the Ten-Year Period 1938-1947

CLAUDE E. WELCH, M.D.,[†] AND ARTHUR W. ALLEN, M.D.[‡]

BOSTON

GASTRIC ulcer has been recognized as a clinical entity for many years. However, it is so closely related to duodenal ulcer on the one hand and gastric cancer on the other that various authorities tend to emphasize either the benign or the malignant aspect to the exclusion of the other. Obviously, in the former case, gastric ulcer would become a minor subdivision of peptic ulcer, and the surgical treatment would consist of control of the complications. In the latter, gastric ulcers are regarded as actually malignant, or so similar to gastric cancer that all should be operated on and the only remaining problems are technical details involved in gastric resection.

Therefore it has seemed important to re-examine the management of patients with gastric ulcer on the basis of the cases studied in the Massachusetts General Hospital during the ten-year period 1938-1947. Additional knowledge of several aspects of the problem has been gained during this time. The most important include a study of the ulcer-cancer relation, the treatment of the most common complication of gastric ulcer (hemorrhage) and the development of a satisfactory operative technic, especially for ulcers about the cardia.

GENERAL CONSIDERATIONS

The diagnosis of gastric ulcer was made in a total of 512 patients in this period (Table 1). Acute perforations have been excluded, since later study has proved that many of them actually are due to duodenal rather than gastric ulcer. The average age at admission to the hospital was fifty-five years, the distribution according to age groups being as follows: ten to nineteen, 0.6 per cent, twenty to twenty-nine, 2.8 per cent, thirty to thirty-nine, 8.4 per cent, forty to forty-nine, 20.4 per cent, fifty to fifty-nine, 32.4 per cent, sixty to sixty-nine, 22.8 per cent, seventy to seventy-nine, 12.2 per cent,

and eighty to eighty-nine, 0.4 per cent. About an eighth of the patients appeared before forty years of age, and an eighth after seventy. Since the duration of symptoms before admission averaged approximately five years, the average age at onset was fifty. Gastric ulcer therefore is essentially a disease of the older age groups, in contrast to duo-

TABLE 1 *Distribution of Cases of Gastric Ulcer*

TREATMENT	1938-1942	1943-1947	TOTALS
Medical	113	104	217
Surgical	104	191	295
Totals	217	295	512
Percentage of operations	48	65	58

denal ulcer, in which the average age at onset of symptoms is about thirty.

The disease is almost exactly three times as common in males (74 per cent) as it is in females (26 per cent).

PROBLEM OF ULCER AND CANCER

Early studies by Holmes and Hampton¹ indicated that all prepyloric ulcerations were malignant, and Sproull² proved the extreme rarity of benign ulcer on the greater curvature. In recent years, improved x-ray technics and the use of the gastroscope have demonstrated many ulcers that would have been overlooked twenty years ago. Coincidentally, there has been a great increase in the number of gastric resection so that histologic confirmation of the clinical diagnosis has been possible much more frequently than it was heretofore.

It is clear that the greater the number of resections the more accurate will be the estimated error in the diagnosis of cancer. For in some cases treated medically as benign ulcer the patients will certainly die of cancer of the stomach, but only rarely can these patients be followed long or closely

*Presented at the annual meeting of the New England Surgical Society, New Haven, Connecticut, October 1, 1948.

[†]Clinical associate in surgery, Harvard Medical School; associate visiting surgeon, Massachusetts General Hospital.

[‡]Consultant in surgery, Massachusetts General Hospital.

The *World List of Scientific Periodicals*, which is not generally used to any great extent in the United States, is employed by the author instead of the abbreviations of the *Quarterly Cumulative Index Medicus* and the *Index Catalogue*, which are commonly used in this country. In the chapter on medical terminology there is a large vocabulary, comprising over 2000 medical terms, arranged by sixteen subjects. This list would have been more useful if all the terms had been arranged in one alphabet. The volume is well published. The work is intended as a student's textbook in teaching institutions, presenting courses for medical secretaries, office assistants and laboratory technicians. The book should prove useful also to all medical secretaries and should be in all medical libraries as a reference text.

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The presence of an accompanying active duodenal ulcer is strong evidence that the gastric ulcer is benign. Figures from the Mayo Clinic^{7, 8} indicate that 0.1 per cent of patients with duodenal ulcer will have carcinoma of the stomach, and 1 per cent of those with duodenal ulcer will have an associated benign ulcer of the stomach.

The presence of multiple gastric ulcers also suggests that the lesions are benign. However, all combinations of ulcer and cancer are seen occasionally, with multiple benign ulcers, associated benign duodenal or gastric ulcer and distinct carcinoma, and multiple ulcerating carcinomas.

In this series multiple gastric ulcers were found in 8 per cent of the patients. Four distinct ulcers were present in one case. Four per cent of the patients had associated gastric and duodenal ulcers.

COMPLICATIONS OF GASTRIC ULCERATION

Incidence

Massive hemorrhage appears to be slightly less frequent with malignant ulcers than with benign since it occurred in only 6 per cent of the cases of ulcer-cancer, compared with benign ulcer, in which the incidence was 9 per cent. On the other hand, pyloric obstruction was much more common, occurring in 19 per cent of the ulcer-cancer group, and in only 1.2 per cent of the benign cases. Perforations, nearly always walled off by adjacent viscera, occur with about equal frequency in both groups.

RATE OF HEALING

The rate of healing of a gastric ulcer is still regarded as the most reliable differential feature between benign ulcer and cancer. Even this fact is not absolute, since in this series two ulcers apparently healed entirely under hospital care but recurred shortly thereafter, and resection proved them to be carcinoma. These rare cases, however, are exceptions to the rule that only benign ulcers tend to heal rapidly. It is also true that some ulcers that prove to be benign fail to heal in a period of months, especially in the older age groups.

This method of differentiation has been applied in a large number of cases in this hospital. In patients that have done well under medical management, significant improvement is usually apparent after a three-week interval. Although complete healing is rare at this time, it occasionally occurs. The average ulcer has healed completely in two months, although at times as long a period as four months is required before the lesion entirely disappears. Consequently, the decision to abandon or continue medical treatment must usually be made a month after the patient is admitted to the hospital. In individual cases, especially in older patients, it may be necessary to wait longer for heal-

ing. Such patients must be followed closely, however, until healing is complete.

The proponents of immediate operation for all gastric ulcers⁹ maintain that this delay is very dangerous from the point of view of spread of misdiagnosed cancers during the interval. On the other hand, it may be pointed out that since the average duration of symptoms before the patient arrives in the hospital is one and a half years, the relatively short extra delay should impose little hazard.

This point obviously cannot be proved by statistics. But it is of interest that of the patients who were believed to have benign ulcer but who were operated on with a delay of less than one month after reaching the hospital, 40 per cent are living and well five years later, of those who were followed for six months or more and then were found to have cancer at operation, all are dead of the disease.

In summary, it is certain that the differential diagnosis of ulcer and cancer cannot be made by present technics in about 10 per cent of the cases. From the point of view of cancer control all gastric ulcers should therefore be operated on at once. However, with care, it is possible to select a small group that can be managed medically if they are closely followed. Following these principles, 97 per cent of the patients who had resections for gastric ulcer were treated correctly. It is of interest that the 9 patients in this series who were followed an inordinate period before resection (the errors in judgment) were exactly equal in number to the deaths after resection.

Types

The complications of gastric ulcer are the same as those of duodenal ulcer, but vary in certain respects. *Perforation* of a chronic gastric ulcer along the lesser curvature is nearly always so gradual that the liver or pancreas walls off the lesion so closely that a general peritonitis does not occur. On the other hand, perforations of so-called acute gastric ulcers close to the pylorus are nearly all duodenal perforations. These free perforations into the peritoneal cavity follow the same course, whether they originate on the duodenal or gastric side of the pyloric vein. *Obstruction* may occur either at the pylorus or, rarely, at an hourglass constriction. In this series, no cases of the latter type were observed. It should also be noted that though reflex vomiting is common with gastric ulcer, pyloric obstruction significant enough to be noted by x-ray examination is much more likely to be due to duodenal ulcer or gastric cancer than it is to gastric ulcer. The demonstration of a gastric ulcer by x-ray study combined with the clinical findings of partial or total pyloric obstruction is therefore an absolute indication for operation. *Hemorrhage* is by far the most common and important complication, occurring as massive bleeding in almost exactly

enough for a final diagnosis to be made. Consequently, the cases reported below, in which an aggressive surgical attack has led to resections in nearly 60 per cent of the entire series, are especially significant.

In this group, 34 of the 512 cases originally diagnosed as gastric ulcer were finally found to be cancer. This was an over-all diagnostic error of 6.6 per cent. Of the patients who had resections and therefore final diagnoses, 32 out of 295, or 10.8 per cent, were proved to have cancer (Table 2).

TABLE 2 *Error in Diagnosis of Cancer*

GROUP	ORIGINAL DIAGNOSIS OF BENIGN ULCER	FINAL DIAGNOSIS OF CANCER	ERROR IN DIAGNOSIS %
All cases	512	34	6.6
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The absolute diagnostic error therefore now lies between 6.6 and 10.8 per cent, and we believe that it is very near to 10 per cent. Since the error in a previous study was at least 14 per cent,³ there has been definite improvement during the past decade. It is pertinent to inquire why this change has occurred and to discuss briefly the differential diagnosis of benign ulcer and cancer.

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No one appreciates his limitations in this respect more than the radiologist, who realizes his inability to make a microscopical diagnosis. It has therefore become the custom to report this group of ulcers as "gastric ulcer, grossly benign." The gastroscopist is limited in the same fashion. To their interpretations, data of less diagnostic importance may be added, including the duration of symptoms, the location of the lesion, the size of the ulcer, the gastric analysis, the cytologic smear of the gastric contents, the presence or absence of accompanying ulcers or complications, and the rate of healing under medical therapy to help distinguish ulcers that are microscopically benign from ulcers that are microscopically malignant ("ulcer-cancer").

AGE AND DURATION OF SYMPTOMS

A short gastric history in a patient fifty years of age or over is highly suggestive of cancer. The average duration of symptoms in patients with "ulcer-cancer" before entry to the hospital is one

and a half years, compared with a duration of five years in patients with benign ulcers. The duration of symptoms with "ulcer-cancer" varied from less than a month to ten years. The ages varied from twenty-six to seventy-seven years for ulcer-cancer, whereas the average age of the entire group was fifty-one years.

LOCATION OF THE LESION

Increasing accuracy in x-ray technic has resulted in the differentiation of many of the benign ulcers and ulcerating carcinomas, especially in the prepyloric area. At present the diagnosis of benign ulcer in the pyloric and prepyloric areas is nearly as accurate as and the error in diagnosis of cancer not much higher than that of lesions on the mid-lesser curvature. Schatzki and Eyster⁴ have found, in an independent review of the same cases, that the radiologic diagnostic error of gastric lesions throughout the stomach is highest in the region of the cardia, less in the prepyloric area and least along the mid-lesser curvature. It is of interest to note that in the period from 1938 to 1947, 6 benign ulcers of the greater curvature were resected.

SIZE OF THE ULCER

Although previous studies have shown that the incidence of cancer increases with the size of the ulceration, very little attention should be paid to this feature in the individual case. It is apparent that early operation will increase the number of resected small ulcerating carcinomas. In this series, the average diameter of the malignant ulcer was 1.8 cm, and only 1 was over 2.5 cm. The benign ulcers that were resected averaged 1.6 cm, and the largest benign ulcer was 7.0 cm in diameter.

GASTRIC ANALYSIS

The presence of free hydrochloric acid is of no significance although its absence after the use of histamine is strongly suggestive of cancer. Free hydrochloric acid is found in approximately 90 per cent of the patients with benign ulcer and of those with ulcer-cancer. About 40 per cent of carcinomas of the stomach are accompanied by histamine achlorhydria.

CYTOLOGIC SMEAR

A positive Papanicolaou⁵ smear of the gastric sediment demonstrating cancer cells is of immense importance if the interpretation is made by a competent technician. If the smear is positive, the lesion is almost sure to be cancer, since Graham et al.⁶ found only 4 per cent false-positive tests. If the smear is negative, cancer may still be present since approximately a third of the carcinomas of the stomach fail to show cells when usual methods are employed. Careful preparation of specimens diminishes this error,⁶ and it is possible that further experience with such substances as

eugenol will increase the accuracy of this test even more

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No one appreciates his limitations in this respect more than the radiologist, who realizes his inability to make a microscopical diagnosis. It has therefore become the custom to report this group of ulcers as "gastric ulcer, grossly benign." The gastroscopist is limited in the same fashion. To their interpretations, data of less diagnostic importance may be added, including the duration of symptoms, the location of the lesion, the size of the ulcer, the gastric analysis, the cytologic smear of the gastric contents, the presence or absence of accompanying ulcers or complications, and the rate of healing under medical therapy to help distinguish ulcers that are microscopically benign from ulcers that are microscopically malignant ("ulcer-cancer").

AGE AND DURATION OF SYMPTOMS

A short gastric history in a patient fifty years of age or over is highly suggestive of cancer. The average duration of symptoms in patients with "ulcer-cancer" before entry to the hospital is one

and a half years, compared with a duration of five years in patients with benign ulcers. The duration of symptoms with "ulcer-cancer" varied from less than a month to ten years. The ages varied from twenty-six to seventy-seven years for ulcer-cancer, whereas the average age of the entire group was fifty-one years.

LOCATION OF THE LESION

Increasing accuracy in x-ray technic has resulted in the differentiation of many of the benign ulcers and ulcerating carcinomas, especially in the prepyloric area. At present the diagnosis of benign ulcer in the pyloric and prepyloric areas is nearly as accurate as and the error in diagnosis of cancer not much higher than that of lesions on the mid-lesser curvature. Schatzki and Eyster⁴ have found, in an independent review of the same cases, that the radiologic diagnostic error of gastric lesions throughout the stomach is highest in the region of the cardia, less in the prepyloric area and least along the mid-lesser curvature. It is of interest to note that in the period from 1938 to 1947, 6 benign ulcers of the greater curvature were resected.

SIZE OF THE ULCER

Although previous studies have shown that the incidence of cancer increases with the size of the ulceration, very little attention should be paid to this feature in the individual case. It is apparent that early operation will increase the number of resected small ulcerating carcinomas. In this series, the average diameter of the malignant ulcer was 1.8 cm., and only 1 was over 2.5 cm. The benign ulcers that were resected averaged 1.6 cm., and the largest benign ulcer was 7.0 cm. in diameter.

GASTRIC ANALYSIS

The presence of free hydrochloric acid is of no significance although its absence after the use of histamine is strongly suggestive of cancer. Free hydrochloric acid is found in approximately 90 per cent of the patients with benign ulcer and of those with ulcer-cancer. About 40 per cent of carcinomas of the stomach are accompanied by histamine achlorhydria.

CYTOLOGIC SMEAR

A positive Papanicolaou⁵ smear of the gastric sediment demonstrating cancer cells is of immense importance if the interpretation is made by a competent technician. If the smear is positive, the lesion is almost sure to be cancer, since Graham et al.⁶ found only 4 per cent false-positive tests. If the smear is negative, cancer may still be present since approximately a third of the carcinomas of the stomach fail to show cells when usual methods are employed. Careful preparation of specimens diminishes this error,⁶ and it is possible that further experience with such substances as

eugenol will increase the accuracy of this test even more

The presence of an accompanying active duodenal ulcer is strong evidence that the gastric ulcer is benign. Figures from the Mayo Clinic^{7, 8} indicate that 0.1 per cent of patients with duodenal ulcer will have carcinoma of the stomach, and 1 per cent of those with duodenal ulcer will have an associated benign ulcer of the stomach.

The presence of multiple gastric ulcers also suggests that the lesions are benign. However, all combinations of ulcer and cancer are seen occasionally, with multiple benign ulcers, associated benign duodenal or gastric ulcer and distinct carcinoma, and multiple ulcerating carcinomas.

In this series multiple gastric ulcers were found in 8 per cent of the patients. Four distinct ulcers were present in one case. Four per cent of the patients had associated gastric and duodenal ulcers.

COMPLICATIONS OF GASTRIC ULCERATION

Incidence

Massive hemorrhage appears to be slightly less frequent with malignant ulcers than with benign since it occurred in only 6 per cent of the cases of ulcer-cancer, compared with benign ulcer, in which the incidence was 9 per cent. On the other hand, pyloric obstruction was much more common, occurring in 19 per cent of the ulcer-cancer group, and in only 1.2 per cent of the benign cases. Perforations, nearly always walled off by adjacent viscera, occur with about equal frequency in both groups.

RATE OF HEALING

The rate of healing of a gastric ulcer is still regarded as the most reliable differential feature between benign ulcer and cancer. Even this fact is not absolute, since in this series two ulcers apparently healed entirely under hospital care but recurred shortly thereafter, and resection proved them to be carcinoma. These rare cases, however, are exceptions to the rule that only benign ulcers tend to heal rapidly. It is also true that some ulcers that prove to be benign fail to heal in a period of months, especially in the older age groups.

This method of differentiation has been applied in a large number of cases in this hospital. In patients that have done well under medical management, significant improvement is usually apparent after a three-week interval. Although complete healing is rare at this time, it occasionally occurs. The average ulcer has healed completely in two months, although at times as long a period as four months is required before the lesion entirely disappears. Consequently, the decision to abandon or continue medical treatment must usually be made a month after the patient is admitted to the hospital. In individual cases, especially in older patients, it may be necessary to wait longer for heal-

ing. Such patients must be followed closely, however, until healing is complete.

The proponents of immediate operation for all gastric ulcers⁹ maintain that this delay is very dangerous from the point of view of spread of misdiagnosed cancers during the interval. On the other hand, it may be pointed out that since the average duration of symptoms before the patient arrives in the hospital is one and a half years, the relatively short extra delay should impose little hazard.

This point obviously cannot be proved by statistics. But it is of interest that of the patients who were believed to have benign ulcer but who were operated on with a delay of less than one month after reaching the hospital, 40 per cent are living and well five years later, of those who were followed for six months or more and then were found to have cancer at operation, all are dead of the disease.

In summary, it is certain that the differential diagnosis of ulcer and cancer cannot be made by present technics in about 10 per cent of the cases. From the point of view of cancer control all gastric ulcers should therefore be operated on at once. However, with care, it is possible to select a small group that can be managed medically if they are closely followed. Following these principles, 97 per cent of the patients who had resections for gastric ulcer were treated correctly. It is of interest that the 9 patients in this series who were followed an inordinate period before resection (the errors in judgment) were exactly equal in number to the deaths after resection.

Types

The complications of gastric ulcer are the same as those of duodenal ulcer, but vary in certain respects. *Perforation* of a chronic gastric ulcer along the lesser curvature is nearly always so gradual that the liver or pancreas walls off the lesion so closely that a general peritonitis does not occur. On the other hand, perforations of so-called acute gastric ulcers close to the pylorus are nearly all duodenal perforations. These free perforations into the peritoneal cavity follow the same course, whether they originate on the duodenal or gastric side of the pyloric vein. *Obstruction* may occur either at the pylorus or, rarely, at an hourglass constriction. In this series, no cases of the latter type were observed. It should also be noted that though reflex vomiting is common with gastric ulcer, pyloric obstruction significant enough to be noted by x-ray examination is much more likely to be due to duodenal ulcer or gastric cancer than it is to gastric ulcer. The demonstration of a gastric ulcer by x-ray study combined with the clinical findings of partial or total pyloric obstruction is therefore an absolute indication for operation. *Hemorrhage* is by far the most common and important complication, occurring as massive bleeding in almost exactly

the same proportion of cases as with duodenal ulcer¹⁰

A history of hemorrhage of varying degrees of severity was encountered in approximately 30 per cent of this series. On the other hand, evidence of recent bleeding was found in only 16 per cent of the cases. The majority of patients entering with hemorrhage demonstrated by a hemoglobin of less than 10 gm per 100 cc or a red-cell count below 3,000,000 that they had bled severely. The history and further laboratory studies indicated that the anemia was the result of a slow, persistent blood loss in many cases. In the remainder, a total of 46 cases, the hemorrhage had been sudden and massive.

It is extremely important, from a surgical point of view, to segregate these patients with massive hemorrhage. For it is in this group that emergency surgical procedures must often be undertaken as life-saving measures. Although a complete discussion of the management of upper gastrointestinal hemorrhage is impossible in this short survey, the salient features of bleeding gastric ulcers may be noted.

During this period, the attitude toward these cases in the Massachusetts General Hospital has been essentially conservative. Quite in contrast to Stewart's¹¹ aggressive attack, these patients on the wards usually have been admitted to the Medical Service. If bleeding did not stop, or if it recurred, surgical consultation was requested. This simple plan has, in practice, been subject to so many delays that occasionally lives have been lost before operative measures have been instituted. The liaison has been much closer in the private sections so that operative delay has been less. This diversity of opinion has, perhaps fortunately, provided two distinct categories of treatment: one in which operation is reserved for patients whose hospital course demonstrates that they will die otherwise, and the other (described previously by Allen¹⁰), which nearly always demands early operation in the patients over forty-five years of age.

Several facts that have emerged may be stated. The history of a previous hemorrhage does not aid in the determination of the severity of the present episode. Likewise, bleeding that is apparently trivial on entry may develop into massive hemorrhage under observation. Sex does not appear to alter these factors.

The age of the patient is generally believed to be of great importance in prognosis. In this particular group, the number of patients who died from hemorrhage was so small that this factor cannot be assessed significantly. The age of the patients who recovered spontaneously without operation was fifty-seven years, that of those who required surgery to stop the bleeding was also fifty-seven years, and that of the few who died from hemorrhage was sixty-eight years. This may mean

either that hemorrhage is more fatal in old age or that surgery is not requested or advised as frequently in the aged. Furthermore, the age factor is much less important with gastric ulcer, since the incidence of bleeding gastric ulcer below the age of forty-five is very low. Thus, 90 per cent of the massive hemorrhages occurred in patients over forty-five years of age. Of the patients below forty-five, one required an emergency resection, one had an interval resection, and the other recovered spontaneously; there were no deaths in this younger group.

The preoperative diagnosis of gastric ulcer in the presence of massive hemorrhage is often very difficult. Early x-ray studies will show the ulcer in about half the cases, and are of additional value in the elimination of esophageal varices, hiatal hernia or duodenal ulcer as the source of bleeding. The accuracy of x-ray study is increased by later interval examinations, but in 4 cases (9 per cent of those with massive hemorrhage), the ulcer was never demonstrated. Hence, the surgeon, at the time of laparotomy, is often confronted with a stomach that appears entirely normal. He must realize that superficial erosions, especially in the prepyloric area, may bleed massively, and that cirroid aneurysms of the left gastric artery may rupture through microscopic ulcers in the mucosa. Obviously, in these cases, a careful pathological examination will be necessary to establish the diagnosis, and the surgeon is required to explore by a gastrotomy incision or to resect a stomach that appears grossly normal.

Fortunately, gastric resection for actively bleeding gastric ulcer is much less hazardous than that for bleeding duodenal ulcer. This is due to the lack of technical difficulty about the duodenal stump and to the fact that hemorrhage can be controlled in an absolute fashion. Despite the fact that only one of the operations in this group was carried out within forty-eight hours of onset of the hemorrhage, postoperative complications have been rare.

The results in this series may be summarized as follows. 58 patients entered the hospital with gastric ulcer and severe anemia. Four patients died of massive hemorrhage from a gastric ulcer, proved by autopsy, without operation, in retrospect it appears that early surgery might have saved 2 of them. Twenty-eight patients survived without operation, and 26 were operated on during the initial hospital admission. The condition of the majority of the patients had been improved considerably before operation, but in 9 cases operation was carried out as an emergency measure in the presence of active bleeding. There was only one postoperative death, and that followed a late attack on an ulcer that had bled repeatedly on the medical wards.

The over-all death rate from hemorrhage was therefore approximately 9 per cent. In patients

treated surgically it was 4 per cent, whereas in those treated conservatively, it was 12.5 per cent. Consequently, it appears that surgery can be carried out in this group of patients with relatively little hazard and with better results.

It is our belief that there are three groups of patients with gastric ulcer who require emergency operation. A patient admitted with massive upper gastrointestinal bleeding should be given a careful x-ray examination, palpation being avoided, as soon as stabilization has occurred. If a positive diagnosis of gastric ulcer is obtained, and the patient has been bleeding less than forty-eight hours, immediate operation is indicated. If he has been bleeding for a longer time but the hemorrhage stops soon after hospital admission, a period of observation and medical treatment is advised in the expectation that normal blood and nutritional levels may be reached and gastric resection carried out at a time of election. Immediate operation is indicated in this group if a recurrent hemorrhage occurs at any time. In a third, small group, the gastric hemorrhage fails to stop after the patient arrives in the hospital, and operation is indicated soon after his arrival. The same operative indications hold true in the absence of a positive x-ray diagnosis of ulcer provided pathologic lesions of the esophagus, especially varices, and blood dyscrasias can be excluded.

OPERATIONS FOR GASTRIC ULCER

Indications

If it is conceded that any gastric ulcers are to be treated medically, it would be well to define as accurately as possible the groups of patients that are likely to do well and those that will do poorly on conservative therapy. Unfortunately, this is impossible, except in very general terms. An analysis of all the features of the two groups shows that they are nearly exactly similar, and that it cannot be foretold in the great majority of cases what the response to therapy will be. Thus, the sex and age distributions, the location of the ulcer, the incidence of achlorhydria and the presence of occult blood in the stools are strikingly similar. It does appear that the particular ulcers that do poorly on medical treatment are the larger ones, particularly those that are over 2.5 cm in diameter, those that are associated with obstruction, and those that are recurrent with a long history of gastric symptoms.

It is suggested, therefore, that a trial of medical therapy be reserved for patients in whom an excellent radiologist and gastroscopist indicate that the ulcer is grossly benign and who have a duration of symptoms of less than one year, an ulcer that is 1 cm or less in diameter, located on the lesser curvature, and a negative cytologic smear. If the x-ray diagnosis is equivocal or not of the highest

quality, ulcerative lesions in a stomach with histamine achlorhydria or those that are found elsewhere than on the lesser curvature or high in the cardia should also be singled out for immediate surgery. It will be observed that patients with ulcers in the cardia are permitted a period of medical therapy despite the fact that the incidence of cancer is high, this is done because the operative mortality for lesions in this particular location is still great enough to counterbalance the error in diagnosis of cancer. The failure of any of these ulcers to heal, as stressed above, is an absolute indication for surgery.

Types

Any operative procedure for gastric ulcer must satisfy two criteria. It must change the gastric physiology in such a fashion that recurrent ulceration cannot follow, and it must be extensive enough that an adequate operation will have been done if cancer is found on microscopical examination of the specimen. It follows that such operations as gastroenterostomy and vagotomy have no place in the treatment of gastric ulcer, and that some type of gastric resection is indicated when surgery is undertaken.

A satisfactory resection consists of the excision of an adequate section of stomach on either side of the ulcer together with the regional lymph nodes along both curvatures. We believe this is accomplished most satisfactorily by the removal of both the greater and lesser omenta together with at least 50 per cent of the stomach. Furthermore, it has been found that sleeve resections are not satisfactory because the gastric physiology is not altered sufficiently and a recurrent ulcer may occur. Clinical experience has shown that the antral mucosa exerts a great influence on gastric secretion. Thus, if a Finsterer exclusion procedure is carried out for duodenal ulcer, with the line of distal section through the antrum, and with retention of the antral mucosa, a postoperative jejunal ulcer can be expected in nearly every case. It is obvious that this operation is used very rarely for gastric ulcer, since it is usually easier to divide the duodenum. However, it was employed in one case in this series, and the patient thereafter developed a recurrent gastric ulcer near the anastomosis. Relief followed resection of the retained antrum. The importance of the antrum has been confirmed by Ransom,¹² who reported 4 anastomotic ulcers following gastric resection for gastric ulcer, and in 3 of them the resections were incomplete since the antral mucosa was retained.

Resection of the distal portion of the stomach, including the ulcer and at least 2 cm of normal mucosa proximal to it, is possible in most cases. If a narrower margin is necessary because of the proximity of the esophagus, immediate pathological examination with a frozen section is advisable. We

agree with Marshall and Welch¹³ that mobilization of the left gastric artery often makes an apparently high ulcer relatively easy to resect. However, there remains a group of ulcers near the cardia and in the fundus that cannot be excised by this method, and it is this group that now can be treated adequately by resection of the proximal portion of the stomach.

The high ulcers include about 10 per cent of all gastric ulcers. As noted above, increasing experience with this group has shown that the differential diagnosis of cancer over the ulcer is especially difficult in this section of the stomach. Heretofore, only two solutions have been available—total gastric resection and distal partial gastric resection with retention of the high ulcer.

Total gastric resection has been employed, and will continue to be used for certain gastric ulcers that are believed to be extensive carcinoma. The end-results prove, however, that this operation is to be avoided, when possible, for benign lesions.

TABLE 3 *Operative Mortality*

OPERATION	No OF CASES	No OF DEATHS	MORTALITY	
			%	
Partial distal gastrectomy	269	6	2	2
Partial proximal gastrectomy	14	3	21	0
Total gastrectomy	4	0	0	0
Miscellaneous	8	0	0	0
Totals	295	9		
Average			3	0

Varying degrees of malnutrition and anemia, as pointed out by MacDonald, Ingelfinger and Belding,¹⁴ occur postoperatively and have, in certain cases, proved troublesome.

Since the antral mucosa is so important in the formation of ulcers, Madlener¹⁵ suggested that a resection of the distal stomach could be done for a high ulcer with the expectation that it would heal spontaneously thereafter. The operation was revived by Colp,¹⁶ who reported favorable results in 8 cases. This procedure has not found favor elsewhere since it not only fails to eliminate the possibility of cancer but also has not affected healing in certain cicatrized ulcers.

More recently two other methods of attack have been developed. Vagotomy has been suggested as of particular value in the inaccessable group of ulcers. This procedure may give a false sense of security that is quite unjustifiable. We cannot agree that it has any place in the treatment of the lesions that frequently turn out to be cancer.

The final method appears the most logical in this group. It involves a proximal partial gastric resection, including the ulcer, with an esophago-gastric anastomosis. Developed concomitantly with the operative attack on carcinoma of the cardia and lower esophagus, Churchill and Sweet¹⁷

have described the technic that is followed for all lesions in this location. In this series, 14 cases of high gastric ulcer have been treated by this method, chiefly by Dr. Richard H. Sweet.

Theoretically, this operation has several features that will make the late follow-up results of great interest. Thus, the antral mucosa is retained—definitely a hazard in any other type of ulcer operation. Since a vagotomy is automatically done by the nature of the operation, as well as a removal of a large portion of the acid-bearing fundus, it is probable that the ultimate results will prove satisfactory. Studies of gastric secretion of several of these patients are now under investigation by Jones and Culver¹⁸ and will be reported later by them.

Removal of these high ulcers by proximal resection is accompanied by a greater risk than that of partial distal resection and is followed by more post-operative symptoms. Follow-up results have been obtained in 10 of the 11 patients who survived operation. There are no recurrent ulcers in the group. Four are entirely asymptomatic. The others complain of various symptoms that are trivial in 4 and severe in 2. They consist of fullness on the ingestion of small amounts of food, and regurgitation of small amounts of mucus and bile early in the morning.

Complications and Mortality

With the exception of the fatal cases, the postoperative complications were, in general, of little importance. The mortality of partial distal gastric resection was 2.2 per cent (Table 3). The 6 deaths were due to local sepsis (2 cases), pneumonia (2 cases), acute pancreatitis (1 case) and appendicitis with perforation (1 case). After trans-thoracic partial proximal resection the mortality was 21 per cent. There were 3 deaths: 1 patient succumbed of postoperative shock, 1 of coronary thrombosis, and 1 (who also had a resection for carcinoma of the esophagus) of massive pulmonary embolism.

RESULTS

With the exception of the proximal partial gastric resections, no elaborate attempt has been made to carry out complete follow-up studies in this group of patients, since this work is in progress and will be reported elsewhere.¹⁹ The general trends of conservative therapy, however, are indicated in the following figures, comprising the years 1940-1946. Eleven per cent of the entire group of patients did well on medical therapy. In 14 per cent the results were probably good, but were indeterminate since the patients did not return long enough to the outpatient department for us to be sure that the ulcer remained healed. Twenty per cent did poorly and refused further treatment or required surgery.

Surgical therapy was carried out at some time in 58 per cent of the entire series. A small group of 8 patients had miscellaneous operations. Two

had a vagotomy, 1 is apparently cured, whereas the other has a recurrent ulcer. Gastrotomies were carried out in 2 patients, no ulcer being demonstrated, one of them did well, and the other has radiologic and clinical evidence of recurrent ulcer. Three patients had a gastroenterostomy, one of them died later, probably of cancer, another had a massive hemorrhage two years later, and the third has been lost. One patient who had a local excision of an ulcer for massive hemorrhage did well.

Gastric resections were carried out in 295 cases. Four of the patients had a total gastrectomy — loss of weight and inability to maintain nutrition are common in this group. The remainder had partial gastrectomies. After recovery from resection, only 1 patient has required reoperation. That patient, mentioned above, developed a recurrent gastric ulcer following a Finsterer exclusion procedure for massive hemorrhage. One patient developed an anastomotic ulcer two years after an adequate subtotal gastrectomy. This jejunal ulcer responded rapidly to medical therapy. The possibility of an anastomotic ulcer was raised in 3 other cases, but in none could a crater be discovered on x-ray examination and all patients recovered promptly on conservative therapy.

Follow-up studies, still incomplete, indicate that approximately 75 per cent of the patients will be asymptomatic after partial gastric resection. Fifteen per cent will have trivial gastric symptoms, easily controlled by diet. Ten per cent will have symptoms of a small stomach, lack of appetite or gastric distress and loss of strength, endurance or weight that will require medical care. These conclusions agree with those of Ransom,¹² but are slightly less favorable than those of Walters and Clagett,²⁰ who report uniformly excellent results after subtotal resection for gastric ulcer.

SUMMARY AND CONCLUSIONS

Several trends in the management of gastric ulcer have become apparent in the past few years. It has been shown that the term "peptic ulcer" should be eliminated, and that gastric ulcer is a distinct entity not to be confused with duodenal ulcer. It has also been demonstrated that gastric ulcer still cannot be differentiated from cancer in nearly 10 per cent of the cases. Although improved diagnostic methods have tended to reduce this

error, the mortality of operation has simultaneously declined to minimum levels.

To the surgeon interested in cancer control, these tendencies make gastric resection advisable for all gastric ulceration. The physician, on the other hand, is tempted to treat these ulcers medically, stressing the operative mortality, low though it may be, the discomforts of operation and the post-gastrectomy symptoms that may appear.

If medical therapy is elected, such cases must be carefully selected, studied by the best radiologist and gastroscopist available, and followed vigilantly, with early recourse to surgery if healing is not prompt. The physician must realize that new operative techniques provide satisfactory excisional surgery for ulcers of the cardia and that radical surgery for the most common complication of gastric ulcer — hemorrhage — is both safe and desirable.

From the principles outlined above, it appears that surgical therapy is indicated in approximately 75 per cent of the patients with gastric ulcers and that excellent results are to be expected after gastric resections.

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PATHOLOGY AND PATHOGENESIS

A brief description of the pathology of chronic pneumonitis due to mineral oil follows, to call attention to the factors that will enable one to make a clinical diagnosis in the ambulatory adult. It has been shown that the severity of the reaction in the lung to aspirated oil depends upon the character of the oil.¹²⁻¹⁴ When saponifiable oils enter the lower respiratory tract, the type of immediate reaction is due to the amount of fatty acid present or produced from the aspirated oil by tissue enzymes. Mild vegetable oils, like poppy-seed oil, olive and sesame oils cause the least reaction. On the other hand, cod-liver oil, lard and animal fats are capable of producing sudden and violent reactions, with hemorrhage and necrosis. The response of the lung to liquid petrolatum, a non-saponifiable oil, is extremely mild, amounting to a foreign-body reaction to an inert substance within and around the alveoli in which the oil settles. The final stage in this pathologic process is fibrosis of the lung occurring first as a mere thickening and infiltration of the alveolar septum and later going on to form fibrous nodules, some tubercle-like, around large collections of lipid material. A proliferative rather than a necrotizing pneumonia is the rule after repeated aspiration of liquid petrolatum. Occasionally, the proliferative pneumonitis takes on the pathological and x-ray appearance of a circumscribed, uniformly dense tumor mass surrounded by a concentric fibrotic ring to which Ikeda¹⁵ has given the name "paraffinoma."

The presence of free oil in the alveoli in pneumonitis due to mineral oil is so striking that oil may be found at the surface of the preserving fluid shortly after a cut section of the involved lung is placed in a laboratory jar containing the fluid. This phenomenon helped to focus the attention of pathologists on the existence of this uncommon disease.

Microscopically, macrophages filled with oil may be found in the alveolar spaces, in the lymphatics and in the hilar lymph nodes. The last, however, are rarely appreciably enlarged even in the later stages of oil-aspiration pneumonia. Pleural reactions, too, are extremely uncommon, and if they occur are usually secondary to superimposed infection.

It is not difficult to see that the disposition of the aspirated oil is dependent largely upon gravity and inspiration suction. Accordingly, the mineral-oil pneumonitis in the ambulatory adult will be found as a rule at the lung bases, more on the right than the left, and ultimately in both lower-lung fields.

SYMPTOMS, SIGNS AND COURSE

A remarkable paucity of symptoms referable to the respiratory tract is elicited on close questioning, even when the pulmonary involvement is far advanced. Certainly the patient is asymptomatic

when the process in the lungs is in its incipency. It is uncommon for this low-grade pneumonitis to be complicated by symptoms of suppuration of the lungs or bronchiectasis. As might be expected, some of the patients may be subjected to recurrent acute pneumonias superimposed upon the oil pneumonitis. As the pulmonary reaction to the liquid petrolatum piles up to an imposing radiographic appearance, the patient becomes noticeably dyspneic on exertion and may develop a hacking cough. However, because of age, the dyspnea and cough may be attributed to arteriosclerotic heart disease. Or, if the pulmonary disease is discovered for the first time on x-ray study and found to be one sided, a diagnosis of carcinoma of the bronchus may be made.

The striking thing about this benign disease in most ambulatory adults is the good nutrition, comfort and general well-being of the patient in the presence of even extensive pulmonary involvement. Likewise, it is also remarkable that, given the x-ray findings in a proved case of mineral-oil pneumonitis, re-examination of the involved lungs will disclose only scant and unrevealing signs on inspection, percussion and auscultation.

FLUOROSCOPY AND CHEST X-RAY STUDY

The earliest involvement of the lungs by the chronic aspiration of liquid petrolatum causes no localized findings on the chest film or only increased markings. As the oil continues to spill over into the lungs, a small, basal, infiltrative process, looking not unlike a bronchopneumonic lesion, soon appears. At times, the early process seen on the x-ray film has a hard appearance, owing to the intense proliferative reaction around the oil-containing alveoli. The picture, as in one of the cases reported below, may resemble that seen long after bronchography has been done with a radio-opaque oil in the pulmonary area, and a fine residuum of that substance has been left.

As the pneumonitis progresses, the infiltrations fuse into an ill defined area of ground-glass density, or the density may become circumscribed (paraffinoma formation). As a rule, no associated indirect evidence of atelectasis is apparent, nor is hilar adenopathy noted. The latter features are worth bearing in mind in the differentiation of this benign disease from a neoplastic process.

On fluoroscopy, both leaves of the diaphragm move freely, their contour is not appreciably altered, and the heart and the mediastinum are situated in the normal position. Diaphragmatic changes will occur, however, in late oil pneumonitis as a result of secondary infection and compensatory emphysema.

In these ambulatory patients, radiographic extension of the lesion is to be expected as is ultimate involvement of both lung fields while the patient continues on the oil regimen. A sudden regression

PULMONARY HAZARD OF THE INGESTION OF MINERAL OIL IN THE APPARENTLY HEALTHY ADULT

A Clinicoroentgenologic Study, with a Report of Five Cases

LOUIS SCHNEIDER, M D *

MT VERNON, NEW YORK

PERIODIC reports of harm resulting from the ingestion or aspiration of mineral oil have appeared in the medical literature and even in the lay press. Recently, it has been shown that the taking of liquid petrolatum with food prevents substantial amounts of food carotene, a precursor of vitamin A, from entering the body.¹ This fact and some corollaries thereto have been established to the satisfaction of authors of the latest books on nutrition and vitamin therapy and have provoked editorial comment.²

More than two decades have elapsed since it was demonstrated that serious harm can be done to the lungs by the introduction of mineral oil into the nose or throat in pure form or as a vehicle for other medicaments.³ This source of chronic aspiration pneumonitis, or so-called lipid pneumonia, was described as occurring especially in infants and young marantic children.⁴ The use of this hydrocarbon in nose and throat medication was thereupon officially condemned by the New York City Health Department. Soon, intranasal instillation of liquid petrolatum was shown to be equally harmful to adults and children,⁵ and the reversibility of the pulmonary process following the withdrawal of this treatment was demonstrated.

Then it was found that a chronic pneumonitis can be induced by ingestion of mineral oil as a laxative over a long period. Characteristic pulmonary lesions were encountered in debilitated, recumbent and aged persons, in persons suffering from dysphagia of nervous origin and in patients in whom neoplastic or other destructive processes involved the mouth or throat. This accounts for the large series of cases of lipid pneumonia reported from hospitals for the chronically sick⁶ and the aged and infirm,⁷ and wisely led to the abandonment of the use of mineral oil as a habitual laxative for these patients. It is interesting to note in this connection that liquid petrolatum as a laxative has accounted for nearly half the adult cases of oil-aspiration pneumonia reported thus far and that half the series of 264 cases of this pulmonary disease compiled by Sweeney⁸ in 1942 were found in adults.

It is the purpose of this paper to emphasize the pulmonary hazard to apparently healthy and ambulatory adults inherent in the habitual use of mineral oil by ingestion. Indeed, the broncho-

pulmonary process in these persons comes on so insidiously that it may be uncovered only on a tuberculosis case-finding x-ray survey. It is not a new clinicoroentgenologic phenomenon that prolonged ingestion of this hydrocarbon for laxative or other purposes (one patient said he took mineral oil for the tonic effect it had on him — he called it "poor man's olive oil") can cause chronic pneumonitis in the apparently healthy adult. Individual cases in which the diagnosis has not been made ante mortem or preoperatively have been reported even till recently. Commonly if the pneumonitis is one sided in these older adults, the examining physician often makes a diagnosis of bronchogenic carcinoma,^{9, 10} only to find evidence of oil-aspiration pneumonia in the removed lung specimen. It is to be hoped that the index of suspicion of this insidious man-made disease will increase. It is reasonable to conclude that many cases of benign pneumonitis in the apparently healthy are going undetected if 5 such patients have been seen by one observer in a two-year period.

Recently, 2 cases of oil pneumonitis in healthy adults who were normal neurologically except for the finding of an absent gag reflex were reported.¹¹ In 2 other cases, cited below, the gag reflex was markedly diminished, and in still another some dysphagia was associated with the presence of a Zenker diverticulum. Although careful examination of the throat in apparently well older persons might show some abnormality causing the spilling over into the larynx of ingested liquid petrolatum, it has been demonstrated that this substance is so bland that, introduced into the nasopharynx, it can find its way into the lungs without causing symptoms of irritation, such as cough.¹² Serial x-ray films in these cases indicate that it probably takes a long time for a radiologically visible reaction to occur in the lung into which oil aspiration has taken place. Once developed, however, the pneumonitis slowly increases as long as the patient continues on the oil laxative regime. In these apparently healthy persons, only a minute quantity of the oil gets down into the lower order of bronchi at one time, and as time goes on some of it is fortunately removed by expectoration and to a lesser degree by phagocytosis. One patient with lipid pneumonia exhibited no roentgenologically detectable trace of this product in his bronchi shortly after ingestion of 20 cc of iodized oil.

*Chief Chest Service, Washington Heights Chest Clinic, New York City Department of Health, attending physician, Tuberculosis Section, Vanderbilt Clinic.

The first test is an examination of the sputum for oil droplets. This procedure should be carried out some days after the patient has ceased taking mineral oil. Into a clean, wide-mouthed jar, the patient expectorates before breakfast for three successive days after thoroughly washing his mouth and throat with physiologic saline solution. He keeps this jar in the refrigerator concealed in a paper bag so that the contents do not offend the ice-box raider. Two analyses may then be done with this accumulated sputum. If oil droplets are present, placing cigarette paper or a piece of lens paper on the surface of the expectorated material will bring out the tell-tale grease spots on the paper. Now, if a sample of the sputum is examined under the microscope, the contained mineral oil droplets will take the characteristic stain with scarlet red. Saponifiable fats and oils, on the other hand, take the osmic acid stain.

The second confirmatory test is an aspiration biopsy of the affected lung. This procedure when wisely employed is comparatively safe,^{7, 16} the chief danger and discomfort being the induction of a pneumothorax. The region to be punctured is carefully mapped out under fluoroscopic control. Procaine is injected into the skin, and a needle of 16 or 17 bore is plunged quickly into the involved lung parenchyma. Suction should then be applied until a little bloody material is drawn into and mixed with the procaine in the barrel of the syringe. The needle is then just as quickly withdrawn. Holding the syringe vertical for a while against a bright light with the needle upward, one can see oil droplets on the surface of the bloody fluid if the biopsy has been properly performed. In a case of lipid pneumonia, to determine if the oil seen is liquid petrolatum, microscopical examination may then be performed with the use of scarlet-red stain.

TREATMENT

It is clear that the ambulatory adult found to have oil-aspiration pneumonitis is promptly told to discontinue taking mineral oil. As indicated above, early lipid pneumonia changes will ultimately resolve if this source of lung irritation is stopped in time and if there is no neurologic or anatomic defect in the nasopharynx, promoting additional insults to the already damaged pulmonary tissue. Occasionally, a Zenker diverticulum will be found acting as a reservoir for the spilling over of oil into the lower respiratory tract.¹⁷ This should be appropriately treated.

If there is superimposed pulmonary suppuration or bronchiectasis, the treatment may well be the surgical extirpation of the involved lobe or lobes in patients who are good surgical risks. Lobectomy may also be a wise procedure when a patient with proved oil pneumonitis suffers recurrent attacks of acute bronchopneumonia on top of a one-sided

lesion whose likelihood of clearing up after the discontinuance of the oil habit is remote. A less common indication for radical treatment is the concurrent or possibly subsequent development of alveolar cell carcinoma.¹⁸

CASE REPORTS

The following is a brief presentation of 5 cases of oil-aspiration pneumonitis with the pertinent clinicoroentgenologic data. Curiously enough, all patients were men in their sixties, 4 cases may be said to have been picked up on survey chest films, and the benign course of 3 cases has been followed for some time.

CASE 1 H. K., a 67-year-old retired laundry-truck driver, had never had a chest x-ray examination until visited by a

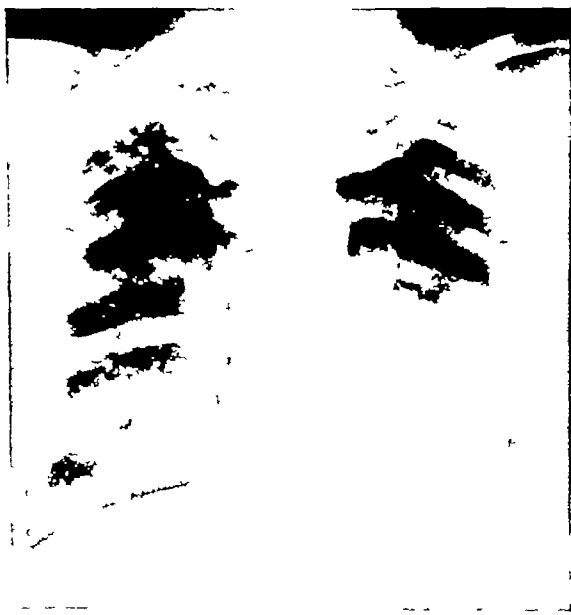


FIGURE 3 Film Taken in Later Examination in Case 2

mobile survey unit in May, 1948. He had had a slight cough, which was often spasmodic for about 20 years. He expectorated a small amount of greenish, nonodorous sputum daily. There was no appreciable dyspnea on exertion or orthopnea. He was subject to infrequent colds associated with a slight fever lasting a few days once or twice a year. No weight change had been noted over the course of years. On the basis of fluoroscopic examinations recently performed, he was told by his physician that the lung changes noted were due to a failing heart.

He had been taking 2 or 3 tablespoonfuls of mineral oil almost daily for the relief of constipation for the past 25 years. He was in the habit of drinking the oil directly from the bottle, and took this medication during the day as well as before retiring. He did not use nose drops. He did not gag or choke when taking anything by mouth.

Physical examination on June 29 disclosed a patient who did not appear acutely or chronically ill. There was moderate clubbing of the fingers and some cyanosis. No cardiac abnormalities were found. Examination of the chest revealed diminished breathing at the right base, no rales were heard. The gag reflex could hardly be elicited.

in the extent of the lesion under these circumstances is usually due to a subsiding acute pneumonitis superimposed upon the chronic process. Once the acute infection is over, the proliferative lung disease will continue its very slow progress. With the discontinuance of this type of laxative habit, early infiltrations have been seen to clear up. How-

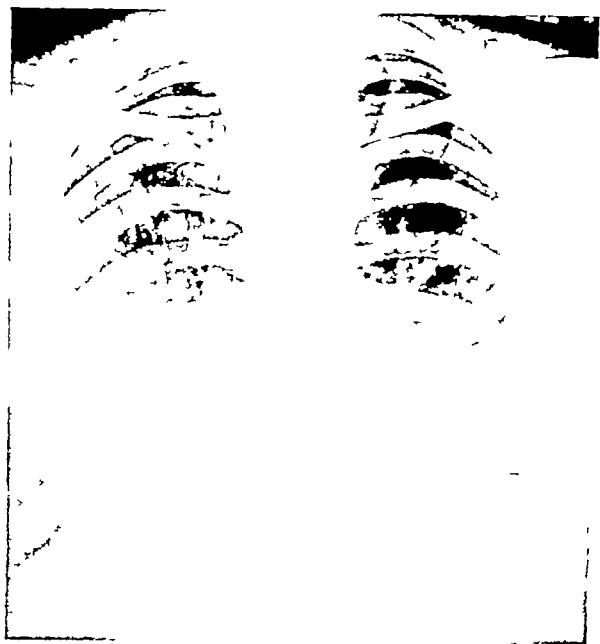


FIGURE 1 *Roentgenogram in Case 1*

ever, the large lesions change little radiographically for years after oil aspiration has ceased.

DIAGNOSIS

Until now the diagnosis of lipid pneumonia has been too frequently a pathological one. In view of the experience presented below, more of these cases will undoubtedly be uncovered by case-finding surveys. With the extension of chest screening to general-hospital admissions, still more cases of oil-aspiration pneumonitis with few symptoms should be uncovered if the index of suspicion of this phenomenon runs high. The importance of making the diagnosis cannot be too strongly stressed, among other reasons, lest a case of this sort be sent to the surgeon for needless lobectomy or pneumonectomy.

A history of regular ingestion of mineral oil should be inquired into when one is dealing with a basal process of undetermined etiology in an otherwise well adult. Certainly, the suspicion of chronic benign pneumonitis due to liquid petrolatum must be seriously considered in the presence of a bilateral lower-lobe process found on a routine chest film of an adult who has few respiratory complaints and

who exhibits few physical signs on examination of the thorax.

The chief difficulty in differential diagnosis occurs when the lesion is unilateral. Then the possibility of neoplasm is uppermost in the mind of the present-day clinician. Contrary to bronchogenic carcinoma, however, in this chronic benign process the x-ray film reveals the lesion to extend peripherally, atelectatic phenomena are absent, and hilar adenopathy is not usually seen. Although carcinoma of the lower respiratory tract can exist with relatively few symptoms referable to the lungs, the cause of the process is less likely to be neoplasm than oil-aspiration pneumonitis, in which negative bronchoscopy is the rule unless there has been supervening infection.

The differentiation of lipid pneumonia in the adult from basal tuberculosis, primary bronchiec-



FIGURE 2 *Routine Film of the Chest Taken on June 10, 1944, in Case 2, Showing an Ill-Defined Infiltration Under and Adjacent to the Left Heart Border and Also an Old, Minimal Lesion at the Right Apex*

tasis or mycotic bronchopulmonary infection is a less difficult task. In these ailments, the symptoms, signs and difference in x-ray shadows are usually in sharp contrast to those of oil-aspiration pneumonitis. In addition, the examination of the sputum for specific organisms and the character and quantity of the expectoration will clinch the diagnosis of these chronic infections.

Two certain confirmatory tests have been used in the diagnosis. Both are based on the pathological finding that mineral oil remains in the alveoli long after aspiration into the affected lung has ceased.

may be that he invariably went to sleep on his left side shortly after taking his usual nightcap of mineral oil

CASE 3 S D, a 60-year-old Negro porter, first came under observation when given a routine x-ray examination in an effort to trace the possible source case to his son, who had died of pulmonary tuberculosis in January, 1948

The patient had no cough or other respiratory symptoms His appetite had been good His occupation had always been that of porter There had been no exposure to noxious dusts He had not been using nose drops For the past three winters he had been in the habit of taking a tablespoonful of mineral oil daily after breakfast He had also been taking this hydrocarbon at infrequent intervals in the other seasons of the year

Physical examination disclosed no abnormal findings except for slight malnutrition and a markedly diminished gag reflex The sputum was negative for tubercle bacilli and positive for oil droplets grossly and microscopically X-ray study of the chest on May 17, 1948, showed a fine nodular lesion in the left-lower-lung field anteriorly between the level of the fourth and sixth ribs (Fig 4) The appearance of the process was not unlike that seen some time after bronchoscopy when incompletely expectorated iodized oil has been left in a number of the alveoli

The interesting feature of this case is that it probably represented an early completely asymptomatic oil-aspiration pneumonitis Much less of the hydrocarbon had been aspirated into the lungs in this case than in the previous ones All that is needed here is the prompt recognition of the cause of the pulmonary lesion and asking the patient to desist from taking any more mineral oil In view of the paucity of the pulmonary reaction there is a likelihood that the left-lung lesion will become reversible to a great extent after some time once the oil ingestion habit has ceased

Unfortunately, the recovery of oil in the sputum or by lung puncture in the following 2 cases could not be obtained, owing to nonco-operation However, the clinicorontgenologic course, the history and the very long follow-up study have left no doubt in my mind, or in those of many groups of radiologists and phthisiologists to whom the films have been shown, that these are also excellent examples of insidiously developing pulmonary granulomas due to chronic aspiration of mineral oil taken for laxative purposes

CASE 4* H S, a 63-year-old real-estate operator, had been followed for 2 years since the discontinuance of the mineral-oil habit

The pulmonary lesions had been discovered in a case-finding survey done on June 17, 1946 This film and an oblique view taken on the same day showed a large area of ground-glass density confined to the right middle lobe and a small, less well defined area of similar character in the left-lower-lobe region just above the diaphragm (Fig 5) A diagnosis of carcinoma of the lung was made elsewhere, and the patient was in a greatly wrought-up condition over the concern shown him because of the accidental findings in the chest film

It was believed that the bilateral process spoke against carcinoma, as did also the almost complete absence of symptoms and signs and the apparent excellent preservation of health An absent gag reflex was also noted

On careful questioning the patient gave a history of taking mineral oil for constipation for the past 20 years Hardly a day had passed, according to this patient, without his tak-

*This case has been reported elsewhere.¹¹

ing about 2 ounces of liquid petrolatum, which he often drank from the bottle This preparation was consumed both day and night He took no nose drops and had no dysphagia

A film taken 2 years after the discontinuance of the mineral-oil habit showed no appreciable change in the extent or character of the pulmonary lesions that had been revealed on the original x-ray survey His general health remained excellent

The diffuse fibrosis characterizing this case of long-standing oil pneumonitis is obviously not reversible, as indicated by serial films taken over a two-year period Nevertheless, since the patient discontinued taking liquid petrolatum his health has remained good, and he has had no intercurrent illnesses, respiratory or otherwise Altogether, he has



TABLE 6 Roentgenogram Taken on August 15, 1935, in Case 5

been none the worse for the mild disease of his own creation He considered it therefore a cruel imposition to make him give up mineral oil of which he was fond beyond its laxative effect Breaking this habit in time, however, may have saved him from more serious and enveloping lung changes in the future

CASE 5 H C, a 60-year-old bookkeeper, was referred for bronchography because of obscure bilateral basal pulmonary lesions, more marked on the right side He gave a history of repeated attacks of bronchopneumonia for the past 12 years After an early one of these acute infections, a chest x-ray film on August 15, 1935, showed nothing more than heavily increased markings more prominent in the region of the left lower lobe than elsewhere (Fig 6) Numerous serial films since then had disclosed a slowly spreading right basal lesion, which was dense in its lower aspect and fluffy as it approached the normal portion of the lung above In addition they revealed a less pronounced, spreading, infiltrative process at the left base (Fig 7)

In recent years the patient had noticed increasing dyspnea on exertion, some cough and expectoration and a slight obstruction to the passage of food in the upper throat Many

X-ray study of the chest showed a diffuse conglomerate infiltration in the lower half of both lungs, denser and more marked on the right side (Fig 1). There was a suspicious area of central necrosis within the right basal lesion. On fluoroscopy both leaves of the diaphragm appeared smooth and moved freely. The right costophrenic sinus was obliterated.

Examination of the blood revealed a slight secondary polycythemia. The sputum was negative for tubercle bacilli. Some days after the ingestion of oil had been discontinued,

lesion at the right apex. No respiratory symptoms or lung signs were noted at that time. At a later admission during the summer of 1947 the patient complained of a slight cough, and a chest film showed a very large, uniformly dense and sharply circumscribed lesion (Fig 3) in the left-lower-lobe area, the infiltration in the lobe having coalesced and giving the appearance of a uniformly dense, discrete mass (parafinoma). A provisional diagnosis of bronchial neoplasm was made. Bronchoscopy showed only a thickened, congested and narrowed left bronchus, and a Papanicolaou smear of the sputum was negative.

When this patient was seen on a routine visit in April, 1948, the examiner was impressed with the fact that the left basal lesion had progressed only slightly on serial x-ray study since the preceding July. Furthermore, the patient looked too well and comfortable for a person ill with a bronchial carcinoma of that size of at least 1 year's duration. Close questioning disclosed that he had been taking 2 tablespoonfuls of mineral oil regularly at night for the previous 10 years. He was thereupon readmitted to the hospital for aspiration biopsy of the left lower lobe under fluoroscopic control, according to the method outlined above. He stood the procedure well, and there were no ill aftereffects. Free oil droplets were easily found in the fluid withdrawn from the lung on both gross and microscopical examination.

In this case the growth of the lipid-pneumonia lesion could be traced on the x-ray film from its



FIGURE 4 Roentgenogram in Case 3

the patient was asked to bring in some sputum for examination for liquid petrolatum, in accordance with the procedure outlined. The sputum was thick and greenish and had no odor. The presence of mineral-oil droplets was readily demonstrated microscopically.

This was probably a long-standing case of lipid pneumonia. Secondary suppuration was undoubtedly present, characterized by the expectoration of purulent sputum, the x-ray picture of the right base and the clubbing of the fingers. The typical distribution of the process in this ambulatory patient and the paucity of physical signs are worth noting, as is the ease with which mineral oil was found in the sputum.

CASE 2 E Y, a 64-year-old unemployed laborer, had had numerous hospital admissions for nondisabling rheumatoid arthritis and had recently developed arteriosclerotic heart disease with congestive failure. At present he was an ambulatory patient receiving weekly injections of mercurial diuretics and complained of nothing more than some dyspnea on exertion.

During one of his sojourns in the hospital a routine chest film done on June 10, 1944, revealed, in addition to the presence of a slightly enlarged heart, a scattered infiltrative process adjacent to the left cardiac border that appeared to be emerging from underneath the left side of the heart (Fig 2). There was also an old, minimal, fibrocalcific tuberculous

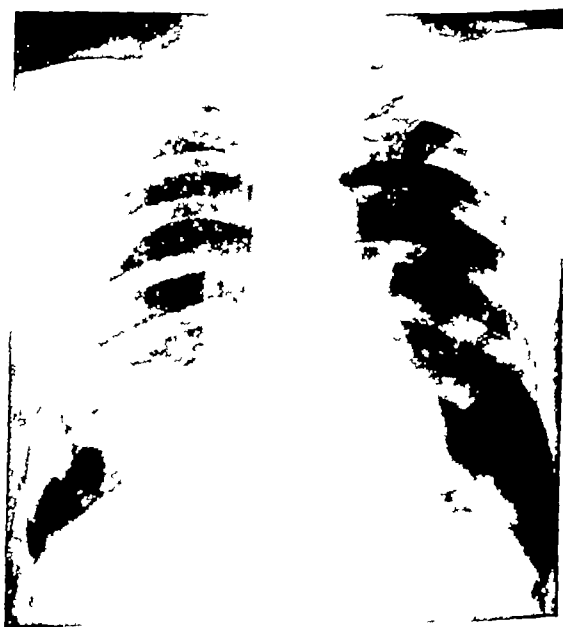


FIGURE 5 Roentgenogram in Case 4

The mesh-like fibrosis in the right middle lobe, as well as above the left leaf of the diaphragm, presents a different appearance from that in the previous cases

early beginnings as a nondescript basal infiltration to subsequent discrete tumor formation. The ease with which free oil was found on needle biopsy that helped clinch the diagnosis is also worth noting. If the disposition of the aspirated oil depends on gravity one expects the basal pneumonitis to be more likely on the right than the left side. A possible explanation for the fact that the pulmonary involvement was located exclusively on the left

of the pulmonary hazard to the habitual users of this bland laxative

Since this paper was submitted for publication, 2 additional cases of oil-aspiration pneumonitis in ambulatory adults who had been taking liquid petrolatum as a laxative for many years have been encountered, one was seen in consultation because of a history of repeated episodes of low-grade lower respiratory infections, and the other, picked up on survey, had a small, circumscribed lesion (paraffinoma) at the right base diagnosed as lung tumor preoperatively

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COMPLICATIONS FOLLOWING PARAVERTEBRAL LUMBAR SYMPATHETIC BLOCK WITH NUPERCALINE IN OIL*

Report of a Case

JACOB T. BRADSHER, JR., M.D.†

BOSTON

THE complications following the use of procaine and procaine-like compounds in producing therapeutic and diagnostic paravertebral lumbar sympathetic blocks are infrequently reported in the literature. However, the relation of the sympathetic chain to the spinal cord and the major vessels in much of its course, the relatively poorly controlled method of placing the anesthetic solution around the chain and the toxicity of the anesthetic agents used make the procedure occasionally hazardous.

Shumacker,¹ in his experiments with guinea pigs, found the median lethal dose of procaine (USP) when injected into the lumbar paravertebral area to be half the subcutaneous dose. He also reported 2 clinical cases of shock-like episodes following the use of procaine for paravertebral lumbar sympathetic block.² From his observations, Shumacker² believed that the aged tolerate local anesthetic agents less well than the young do.

Although the subarachnoid space was occasionally entered during use of the paravertebral sympathetic block before the case reported below, this has been easily recognized by the usual precautions and without ill effect. Entry into the subarachnoid space seems to be more common when the needle is directed cephalad.³ Adelman and Irwin⁴ reported 2 nonfatal cases of aseptic meningitis in young white men following paravertebral lumbar sympathetic blocks using 30 cc of 1 per cent procaine solution in each case. The spinal fluids

showed, respectively, 4000 and 3485 leukocytes, predominantly polymorphonuclears, per cubic millimeter. The spinal-fluid sugars were normal in both cases. Smears and cultures for organisms were negative. The meningitis was interpreted as being due to a chemical irritation produced by pyrogens in the distilled water of the solution used. Aseptic or chemical meningitis following spinal anesthesia was reported by Orkin⁵ as occurring in 0.26 per cent of 45,966 cases collected from the reports of twenty authors. Livingstone et al.⁶ described 2 cases of chemical meningitis following spinal anesthesia and also reviewed 8 other case reports of the same complication. Of the 8 cases, 2 had followed the use of nupercaine, 4 procaine only, 1 procaine and epinephrine, and 1 procaine and strychnine. In this group there were 3 deaths: 1 after nupercaine, and 2 after procaine anesthesia.

The following is a case report describing complications without recovery after a paravertebral lumbar sympathetic block using nupercaine in oil.

CASE REPORT

N. R., an 87-year-old widower, entered the hospital on April 20, 1948. About 1 week prior to admission a small "infection" had developed over the first metatarsophalangeal joint of the right foot. Five days before admission he burned his foot with a hot bath. He gave no history of diabetes by name and symptoms.

The past history revealed occasional ankle edema for the past few years. The remainder of the history was irrelevant.

Physical examination showed a well preserved, small, alert and co-operative man who had a poor memory. The dorsum of the right foot was red, swollen and tender. At the base of the toes there was a linear, depressed, darkly crusted area measuring 5 by 2 cm. Overlying the first metatarsophalangeal joint on the right was an oval, blackish area over 0.5

*From the Fifth Surgical Service, Boston City Hospital.

†Assistant resident, Boston City Hospital.

radiologists and chest clinicians had seen him in the course of years, but no working diagnosis of the pulmonary lesion had been made. Bronchoscopy yielded negative results, as did sputum examinations. When he appeared for bronchography 12 years after the initial study, he gave a history of having taken mineral oil nightly in doses of about 1 ounce regularly for over 15 years. Instillation of iodized oil on July 12, 1947, showed distorted and obstructed bronchi in



FIGURE 7 Roentgenogram in Case 5 Taken Ten Years after That in Figure 6, Showing Upward and Conglomerate Progression of the Lesion

Note the very dense process on the right and the infiltrative lesion on the left

the region of both lower-lobe granulomas and the surprising accidental finding of a Zenker diverticulum (Fig 8)

This case is similar to the one reported by Tchertkoff,¹⁷ which subsequently came to autopsy and showed the typical findings of mineral-oil pneumonitis. The latest films demonstrated a more extensive involvement than that in any of the other patients described above. This is accounted for in part at least by the frequently superimposed pneumonias from which the patient suffered. Unfortunately for him, the cause of the basal pulmonary disease was not established till more than a decade after he came under observation. He has now ceased taking mineral oil for a year, the chest picture has remained unaltered, and his symptoms are practically unchanged. Operative removal of the Zenker diverticulum has been contemplated. The accidental finding of this pulsion diverticulum may be attributed to the fact that the bronchogram was done by the supraglottic route rather than via catheter.

SUMMARY

A typical clinicoroentgenologic picture occurring in some ambulatory older patients who have been habitually taking mineral oil for laxative purposes is described.

The gravitational distribution of the lesions and the paucity of symptoms and physical signs, at least in the early phases of this man-made disease, are emphasized.

It appears clear that it takes some time for a roentgenologically evident pulmonary reaction to this bland, liquid foreign body to develop.

Because of the age of these patients, if the lesion due to the aspiration of liquid petrolatum is one-sided, the common error is made of calling this benign disease a malignant neoplasm and subject-



FIGURE 8 Roentgenogram Taken on July 12, 1947, in Case 5, Showing Further Progression of the Lesion

ing the patient to needless lobectomy or pneumonectomy.

Because 3 of the 5 cases were picked up on tuberculosis case-finding surveys and because all 5 were seen within a two-year period, it is predicted that many more such cases will be discovered in older population groups if the index of suspicion of the disease remains high.

In view of this experience, a chest survey of well adults who take mineral oil for the relief of constipation is being undertaken to ascertain the extent

showed no change from normal until the day following injection when it became elevated. There were no marked changes in the character of the pulse, except for some increase in rate after the temperature began to rise. It seems safe to assume that the phenol played no important part in the patient's reaction.

Benzyl alcohol (phenyl carbinol) is relatively nontoxic, being rapidly converted to hippuric acid in the body.⁹ It is irritating and somewhat corrosive as pure substance, but the watery solutions that contain up to 4 per cent are not. In all proportions it is soluble in oil and is somewhat antiseptic. In dogs spinal anesthesia has been produced by 2 to 4 per cent solutions in saline or oil.¹⁰ Aqueous solutions have only brief anesthetic action, and the anesthesia produced is uncertain. It seems unlikely that, except for some possible transient anesthesia and a questionable irritation of the leptomeninges, the benzyl alcohol was responsible for any of the symptoms presented in this case.

Oil of sweet almond (*oleum amygdalae expressum*) is one of the fixed fatty oils and considered nontoxic and nonirritating.¹¹ Lipiodol, which is iodized poppy-seed oil containing about 40 per cent iodine in organic combination, when injected intrathecally is said to cause a well marked transitory aseptic meningitis with symptoms of meningeal irritation.¹² Boyd¹³ states that degenerative changes in the gray matter and thrombosis of the vessels of the anterior horns may also occur. The oil of sweet almond may have been responsible for some of the cellular reaction seen in the spinal fluid.

Nupercaine is the most toxic of the commonly employed anesthetics, and on intravenous injection is six times as toxic as cocaine.¹⁴ Clinical toxicity, however, seems to depend upon the concentration, and the extreme dilutions used for spinal anesthesia result in very little evidence of toxicity. The dosages for spinal anesthesia vary between 6 and 10 mg. Nupercaine is more rapidly absorbed from the subarachnoid space than from any area (except after intravenous administration).¹⁵ The most prominent toxic effects of nupercaine are on the circulatory system and are more pronounced than those from any of the other commonly employed spinal anesthetics.¹⁶ Bieter et al.,¹⁷ experimenting with spinal anesthesia in rabbits, observed irritant or toxic symptoms with ocular complications, convulsions and spasticity of the head, neck and forelegs. Of the procaine and procaine-like compounds used, nupercaine and pantocaine (tetracaine hydrochloride, *USP*) showed the toxic effects most frequently. Davis and his associates,¹⁸ using nupercaine, procaine and similar compounds intrathecally in dogs, found the most constant change to be an aseptic meningeal reaction. For the most part, the exudates were of the lymphocytic type. The authors also observed degenerative changes in the spinal cord.

In the case reported above, the initial fall of blood pressure, with the pulse remaining at near normal levels, frequently seen with spinal anesthesia, was probably the result of absorption of nupercaine from the spinal canal. The response to the sympathomimetic agent is somewhat confirmatory. Since the level of anesthesia never rose above the umbilicus and there was no evidence of respiratory paralysis, it can be assumed that the later stupor and convulsive movements of the arms were systemic reactions to the nupercaine similar to the reactions described by Shumacker.² Control of the clonic movements by barbiturates favors this explanation. In view of the experiments of Davis,¹⁸ Orkin⁵ and Livingston,⁶ one is led to believe that the nupercaine was chiefly responsible for the meningeal reaction.

The increasing stupor and changes of respiration during the day before death probably were signs of increasing reaction.

SUMMARY

A case is reported of an elderly man who, having shown a good peripheral vascular response to two previous paravertebral lumbar sympathetic blocks, developed motor and sensory changes, circulatory depression, stupor, convulsive movements of the upper extremities and late signs of meningeal irritation with death after a third block, using nupercaine in oil. The nupercaine seemed to be the chief causative agent, with possible added effects of the phenol, benzyl alcohol and oil of sweet almond — other ingredients of the solution used.

818 Harrison Avenue

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cm in diameter. The dorsalis pedis and posterior tibial pulsations were faintly palpable bilaterally. The radial arteries were sclerotic and tortuous, with marked beading. The heart was normal except for an occasional premature systole. The chest was narrow, and a moderate dorsal kyphosis was present. The lung fields were clear to percussion and auscultation.

The temperature was 98.6°F, the pulse 84, and the respirations 20. The blood pressure was 156/88.

Examination of the blood revealed a hemoglobin of 50 per cent and a white-cell count of 8700. The urine had a specific gravity of 1.015, was free of sugar and showed a ++ reaction for albumin, and the sediment contained many white cells and a few white-cell casts. The nonprotein nitrogen was 34 mg per 100 cc. The fasting blood sugar level was 80 mg per 100 cc. The blood Hinton test was negative.

The patient was placed on bed rest and given intramuscular injections of penicillin. It was believed that hot wet packs to the foot and leg were indicated. After 1 day the condition of the foot seemed worse, and examination revealed that no dorsalis pedis or posterior tibial pulsations were palpable. The hot wet packs were discontinued, and moist boric dressings were instituted. The cellulitis subsided, but healing was slow. The first and second toes began to show some dark discoloration. It was decided to perform a right paravertebral lumbar block. The block was performed 5 days after entry according to the method of White and Smithwick,⁷ using 40 cc of 1 per cent procaine solution. The procedure was followed by improvement in the color and increase of temperature of the foot. Four days later a second block was performed. This time nupercaine in oil was used in an attempt to prolong the effect. A total of 10 cc of the solution was used, containing 50 mg of nupercaine. The improvement of the circulation to the foot was prolonged. On the 12th hospital day a third block was attempted. With the patient in the left lateral recumbent position, 20-gauge spinal needles were placed at the level of the first, second, third and fourth lumbar vertebrae. There was no evidence that the subarachnoid space had been entered, aspiration at each level yielding no spinal fluid. At each site 2.5 cc of nupercaine in oil was injected — a total of 10 cc (50 mg of nupercaine hydrochloride). Shortly after the injections the patient began complaining of "numbness" in both legs and then of inability to move either leg. A level of sensory anesthesia was identified just below the umbilicus. The patient was placed in the sitting position. There was no further rise in the level of the sensory anesthesia. Within a few minutes he complained of feeling faint, and he became pallid. The blood pressure dropped to 40 systolic, nearly 0 diastolic. The pulse was 90 and regular. The respirations remained slow and regular. Two minims of 0.5 per cent neosynephrin was given intravenously, with a resulting rise of the blood pressure to 220/120. Gradually the patient became somewhat stuporous, responding poorly. Nasal administration of oxygen was started. The blood pressure returned to 140/80. The pulse was 84. The blood pressure and pulse then remained stabilized. About 40 minutes after the injection of the nupercaine, the patient developed clonic movements of the upper extremities, which were relieved by the intravenous administration of 0.16 gm of sodium phenobarbital. The clonic movements recurred after 2 hours, and another 0.064 gm of sodium phenobarbital was given. Respirations were regular, varying between 20 and 24.

On the following day the patient remained drowsy and rather disoriented, this was thought to be largely due to the barbiturates that he had received. Motion and sensations returned to the left leg, but there was still a motor paralysis and anesthesia of the right leg. The blood pressure and pulse remained normal. The temperature rose to 101°F. Two days after the paravertebral lumbar injection the patient became quite stuporous and could be roused only by painful stimuli. The temperature rose no higher than 100°F, but the pulse ranged between 100 and 110. On the 4th day after injection the patient continued in a stuporous state. The temperature rose to 101°F by axilla. He was maintained on intravenous fluids and had a urinary output of 2000 cc in 24 hours. The nonprotein nitrogen on this day was 70 mg per 100 cc. It was noted that cervical rigidity had developed and that he winced when the neck was flexed. He moved both extremities at this time. Other findings were flattening of the nasolabial fold on the right, no sensory response below the neck and absent

abdominal, patellar and calcaneal tendon reflexes. The Babinski response was present bilaterally.

A lumbar puncture was performed in the third interspace. The initial spinal-fluid pressure was equivalent to less than 50 mm of water. The fluid was cloudy yellow, had a faint odor of the nupercaine-in-oil solution (oil of sweet almond) and clotted on standing. There were 4060 white cells per cubic millimeter, of which 84 per cent were polymorphonuclear neutrophils and 16 per cent were lymphocytes. A stained smear of the fluid demonstrated no organisms. The protein content of the fluid was 800 mg per 100 cc. Insufficient quantity of fluid was obtained to determine the sugar content. Culture demonstrated no growth on blood agar. Twenty thousand units of penicillin was injected intratheca. One hundred thousand units of penicillin was given parenterally every 3 hours, and 5 gm of sulfadiazine was given intravenously in 3000 cc of fluid. The temperature rose to 104.6°F by rectum. The respirations became labored and shallow. At 7:30 a.m. on April 5 — 4 days after the last paravertebral lumbar injection — the patient died.

Permission for autopsy was obtained, but the body was removed from the hospital prematurely and post-mortem examination was not performed.

DISCUSSION

The agent used makes this case somewhat more complicated than those previously reported. Nupercaine in oil is dispensed in 5-cc vials, a solution of 0.5 per cent nupercaine (25 mg), 1 per cent phenol (50 mg) and 10 per cent benzyl alcohol (0.5 cc) in oil of sweet almond. This preparation is primarily prepared for use in proctologic surgery. The benzyl alcohol and phenol have antipruritic properties, and the phenol also probably aids in reducing the surface tension. Previously, no difficulty with the solution had been encountered in this hospital. One "collapse" reaction, which occurred after a lumbar block, was done with 1 per cent procaine solution in physiologic saline solution.

No reports of the results of injection of phenol into the spinal canal are available. The toxic dose, orally, is given as 8 to 15 gm.⁸ Phenol is a general protoplasmic poison. In toxic amounts it is responsible for shock following widespread capillary damage. The blood pressure falls as a result of central vasomotor depression, but more because of the direct toxic action on the myocardium and finer blood vessels. Cold sweating is prominent, the urine is scanty and contains albumin and casts. Death results from respiratory failure, usually within twenty-four hours. The body temperature falls markedly. In man little central stimulation is observed, and the prominent effects are those of central depression.

The amount of phenol injected in this case would be no more than enough to act as a local anesthetic and irritant. Of the total of 10 cc of solution used, containing 100 mg of phenol, only a small amount probably entered the subarachnoid space. The marked fall in blood pressure that occurred responded quickly to neosynephrin, indicating no widespread injury to the capillaries or finer vessels. Sweating was not seen. Respirations remained regular until four days after the injection. The temperature

seen on culdoscopic examination. The fimbriated end looks as though it were closed by very delicate adhesions that extend outward to the broad ligament and the ovary. The left tube appears essentially the same except that the fimbria are tufted, and apparently open. There are a few adhesions leading from the fimbriated end outward to the broad ligament.

When a cannula is inserted into the uterine cavity, gas apparently does not pass at a pressure under 200 mm of mercury, at 200 mm there is a very slow leak somewhere, with no audible sound at the external os. Possibly, the left tube is patent at high pressure.

DISCUSSION

This patient presented no evidence of tuberculosis other than in the endometrium. It is impossible to say that the disease did not exist elsewhere, particularly in the tubes. Pottenger¹ states that tuberculosis of the uterus is almost always secondary to tuberculosis elsewhere in the body, usually the tubes, and Norris² that the tubes are invariably involved, but most authors give 85 to 90 per cent as the figure.

Data in the literature on the incidence of tuberculosis of the genital tract vary remarkably. Jameson³ gives a table of autopsy findings in women dying of pulmonary tuberculosis. Nineteen authors are quoted, and their figures vary from 1 to 30 per cent, with an average of 9 per cent involvement of the genital organs.

Eichner, Bookatz and Hirsch⁴ found gynecologic tuberculosis in 32 cases when they reviewed 1600 autopsies and 38,000 surgical specimens. They did not state whether these patients had tuberculosis elsewhere except to mention a case of tuberculous meningitis and one with kidney involvement.

In association with sterility, the incidence is apparently higher. Rabau, Halbrecht and Casper⁵ diagnosed tuberculous endometritis by strip curettage in 20 out of 208 sterile women, none of whom had evidence of tuberculosis elsewhere. Vogt (cited by Jameson³) found it in 7 per cent of 212 sterile women, and Jensen and McDonald⁶ in 8 per cent of 25 sterile women. Rock,⁷ at the Free Hospital for Women, Brookline, Massachusetts, observed only 12 cases in 2083 biopsies, an incidence of 0.6 per cent. It has been proved that pregnancy can occur and proceed to term in uteri that are the seat of tuber-

culosis, but Jameson³ believes that the figures regarding sterility in some reported series of genital tuberculosis are not reliable (as low as 17 per cent), in that the pregnancies had probably occurred before the disease was present.

The treatment of genital tuberculosis hitherto has been primarily surgical, although there have been many proponents of x-ray therapy and other measures.

Jameson³ reviews the various forms of treatment and cites a "salvage" of 72 per cent after radical surgery. Te Linde⁸ gives the same figures for "salvage," with a primary mortality of 7 to 9 per cent and cites Greenberg as giving an 11 per cent mortality when there is tuberculous peritonitis, but 2.7 per cent when only the genital organs are involved. According to Jameson,³ the results of medical treatment, x-ray therapy or conservative surgery are even less satisfactory.

SUMMARY

A case of endometrial tuberculosis is presented in which the disease was apparently arrested by streptomycin therapy.

Data from the literature indicate that tuberculosis of the female reproductive organs is not an uncommon cause of sterility.

Although radical surgery is at present the treatment of choice, even when it cures the patient of the disease, it leaves her deprived of her reproductive functions, and often of her ovarian hormones.

It is suggested that further trial of streptomycin therapy in endometrial tuberculosis is warranted.

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STREPTOMYCIN IN THE THERAPY OF TUBERCULOSIS OF THE ENDOMETRIUM*

ALBERT ARANSON, M D,† AND RICHARD W DWIGHT, M D‡

FRAMINGHAM, MASSACHUSETTS

THE apparent arrest of endometrial tuberculosis consequent to treatment with streptomycin, hitherto unreported, appears to warrant the report of the following case

CASE REPORT

C L (CVAH 10,137), a 26-year-old married woman, was referred to Cushing Veterans Administration Hospital by Dr John Rock on November 20, 1947, for the treatment of tuberculous endometritis. She had been well until 1942, when she noted that her menstrual periods, which previously had lasted 4 or 5 days, were prolonged to 8 or 9 days. The flow was not excessive, and the cycle of about 30 days remained unchanged. She also began to have a white, non-odorous vaginal discharge. In April, 1944, she was married. At about this time she began to have vague cramps in both lower quadrants of the abdomen. These occurred irregularly, were not related to her periods and were not sufficiently severe to interfere with her activities. All these symptoms persisted without change until admission. In addition, during the 2 years prior to admission a vesicular rash had appeared on the shoulders at the time of her periods, and she had lost 20 pounds in weight during that time. Late in 1945 she consulted an obstetrician because of her failure to conceive. No cause was found. In July, 1947, she consulted Dr Rock because of sterility. An endometrial biopsy revealed tuberculosis of the endometrium. A second biopsy in September was identical, and she was referred for treatment with streptomycin.

The past history was essentially noncontributory. The patient had had the usual childhood diseases and, in 1939, typhoid fever. There had been no other serious illnesses, and no operations. She had always lived in the eastern part of the United States, and until 1941 in a region where the milk was not pasteurized.

Both parents were living and well. There were no dead siblings and no family history of tuberculosis or history of exposure to it.

She had worked as an accountant prior to service in the WAVES from February, 1943, to January, 1946, and again was working as an accountant.

Physical examination showed a somewhat underdeveloped and undernourished, intelligent, co-operative woman, in no distress. The weight was 130 pounds. The temperature was 98.6°F. The head, neck, eyes and ears were not remarkable, the tonsils were present, but were not inflamed. The teeth were in good condition. The chest was symmetrical, with normal expansion, and the lungs were clear to percussion and auscultation. The abdomen was normal on inspection and palpation, the back and extremities showed no abnormalities. The reflexes were physiologic. There was no enlargement of the lymph nodes. Pelvic examination showed a normal marital introitus, the uterus was normal in size and position, the left ovary palpable but not enlarged, and the right ovary not felt, there were no masses. The cervix appeared normal, there was a moderate amount of slightly frothy yellow vaginal discharge. Rectal examination was negative.

Examination of the urine revealed a trace of albumin on one of twelve examinations but was otherwise negative. The nonprotein nitrogen was 21 mg per 100 cc. The blood Kahn reaction was negative. The red-cell count was 4,100,000, with a hemoglobin of 11.2 gm, and the white-cell count 7900, with 52 per cent segmented neutrophils, 4 per cent band forms, 34 per cent lymphocytes, 8 per cent monocytes and

2 per cent eosinophils, the red cells and platelets were normal in appearance. During the hospital course the hemoglobin ranged from 11.2 to 12.2 gm, the white-cell count between 4100 and 7900, and the hematocrit from 38 to 40 per cent.

Several smears and cultures of the vaginal discharge were negative for acid-fast bacilli, a smear for trichomonas was also negative. An audiogram before treatment was within normal limits. Three x-ray examinations of the chest showed no abnormality.

The tissue section of the endometrial biopsy taken in September was obtained. The report was as follows:

Scattered small tubercles are found, with Langhans' giant cells present. The glands possess a few small papillary projections. The nuclei are predominantly basal. There is slight mucous production. Scattered mitotic figures are observed. There are degenerated neutrophils within the glands. Occasional groups of lymphocytes are seen in the stroma. The pathological diagnosis is tuberculosis of the endometrium.

On November 29 streptomycin therapy, consisting of 0.5 gm intramuscularly every 12 hours, was begun. This was continued for 129 days. There were no untoward symptoms. Audiograms made at 2-week intervals and at the end of treatment showed no loss of hearing. The patient remained in bed except for 1 hour each day. Streptomycin blood levels were determined every 2 weeks. The level was consistently 32 or 64 units per cubic centimeter, except on two occasions when it was 8 and 16 units. Except for a single evening temperature of 100°F, the patient was afebrile. Eosinophil counts during treatment were 2, 2, 11, 9, 3, 3 and 3 per cent. The sedimentation rate was 19, 14 and 20 mm per hour on three examinations.

The vaginal discharge diminished in amount. Three menstrual periods showed the prolonged flow experienced before treatment.

On March 22, 1948, pelvic examination under anesthesia was essentially the same as on admission. The uterus was normal in size and position. The cervix was dilated with ease, the cavity measuring 7 cm deep, smooth and symmetrical. A moderate amount of normal-appearing endometrium was obtained by curettage. One strip of endometrium was used for guinea-pig injection. The animal was killed on May 13, there was no evidence of tuberculosis.

Microscopic examination of the endometrium revealed straight glands with basal nuclei. There was little production of mucus. No tubercles were found, and there was no inflammatory exudate. The diagnosis was normal endometrium, proliferative phase.

The patient was discharged on April 2 and returned on June 1. She had been well and had resumed her work. There had been two menstrual periods with normal flow of 4 or 5 days, the last one on May 14. Dilatation and curettage was performed on June 2. The findings were the same as before, the pathological report showing normal secretory endometrium, with no evidence of tuberculosis. A cervical biopsy was also negative. One piece of endometrium was used for guinea-pig injection. The animal was killed on July 15, and showed no evidence of disease.

The patient was returned to Dr Rock for further study from the point of view of sterility. The following is a condensation of his report of a culdoscopy and insufflation done on July 24:

The fundus is visualized over part of the posterior wall, and part of the summit, and appears normal. There are apparently no adhesions around the uterus. Both ovaries are partly adherent to the broad ligament, but otherwise appear normal. The right tube looks normal, and is seen throughout its length. It varies somewhat in thickness, but not to an unusual degree. The color varies from red to reddish yellow, but this variation is also quite commonly

*From the Medical and Surgical Services, Cushing Veterans Administration Hospital.

†Formerly chief, Tuberculosis Section, Medical Service, Cushing Veterans Administration Hospital.

‡Assistant chief, Surgical Service, Cushing Veterans Administration Hospital.

contained mucopolysaccharides. The latter showed marked hydrolysis when exposed to hyaluronidase, indicating that they were hyaluronic acid. This suggests that pretibial myxedema results from a local disturbance of metabolism of mucopolysaccharides. These authors conclude that the presence of hyaluronidase in the normal thyroid gland and the recent discovery of an enzyme in the blood that destroys hyaluronidase furnish a basis for much speculation regarding the etiology of pretibial myxedema.

Ayres and Jensen¹⁰ report complete cure of the syndrome of otorhinophyma, pruritus and alopecia totalis with testosterone by mouth, 10 mg every one or two days for four months. The patient, a sixty-six-year-old man, had alopecia for fifteen years and later developed a generalized pruritic eruption, with inflammatory hypertrophy of the nose, ears, chin, cheeks and eyebrows, and with dystrophic nails.

After a careful study of the effect of x-ray therapy on rabbit testes, Callaway et al¹¹ conclude that scattered irradiation reaching the gonadal region of the patient receiving low-voltage therapy to the face or other more remote areas is negligible so far as injury to gonadal tissues is concerned.

Ephynal, a synthetic racemic alpha tocopheryl acetate, has been recommended for pruritus due to estrogen imbalance.¹²

Reporting on the spontaneous cure of tinea capitis in puberty, Rothman¹³ proves what has previously been only a theory. He shows that the reason for spontaneous cure in puberty and for adults' immunity to *Microsporum audouinii* infections is that with the onset of puberty the sebaceous glands of the scalp start to secrete a sebum that contains, in higher concentration than before, low-boiling saturated fatty acids with selective fungistatic and fungicidal action on *M. audouinii*. He demonstrates and identifies the low-boiling saturated fatty acids and the normal aliphatic monobasic acids with odd numbers of carbon atoms. The active fatty acids constitute a very small part of the total fat extracted, but such active acids have a minimum fungistatic concentration of 0.0005 per cent. These cures are effected slowly by the sterilization of the follicular canals and the surface of the scalp, preventing further spread, so that as the infected hairs are shed the infection disappears. This article is the result and report of a logical theory, which was tested by exact chemical procedures. Both the experiment and the article describing it are excellent.

The undermining of acne lesions by exteriorization is described by Bereston and Benteen.¹⁴ Treatment consists of excision of the acneform area overlying the cyst or sinus beneath, healing is by granulation and occasionally grafting is indicated. The scarring of the surgical procedure is apt to be extremely disfiguring.

DERMATITIS AND ALLERGY

Klasson¹⁵ reports a study of ascorbic acid in the treatment of poison-oak dermatitis. He believes that vitamin C is capable of preventing and combating the disease. The best results were obtained for the most part in patients with edema of the eyelids and genitalia. This theory certainly needs substantiation. If verified, it would be a boon to outdoor workers.

Epstein¹⁶ adds another theory for the cause of localized bullous dermatitis or benign localized pemphigus — namely, focal infection. Such infection may be a factor in other cutaneous disturbances.

According to Steiner and Fishburn¹⁷ cutaneous eruptions from streptomycin occurred in 18.2 per cent of 33 patients, a marked contrast to 4.9 per cent of 1000 cases reported by Keefer. The temptation is strong to compare these reactions with "ninth-day erythema." Steiner comments that eosinophilia and "accelerated reaction time" on readministration of streptomycin point to the allergic nature of the reactions.

Dermatitis venenata due to streptomycin is frequently seen in nurses administering the drug.¹⁸

Zakon et al¹⁹ report 32 cases of lipstick cheilitis due to a bromfluorescein dye. All were cured by the substitution of lipsticks that contained no halogen derivative of fluorescein.

Discussing the treatment of diaper rash, Benson et al²⁰ recommend diapene (manufactured by Homemakers' Products Corporation), a quaternary ammonium compound (para di-isobutyl-cresoxy-ethoxy-ethyl di-methyl benzyl ammonium chloride monohydrate). Diaper rash is thought to be an ammonia dermatitis caused by decomposition of urea to free ammonia by *B. ammoniagenes* in the feces. Diapene inhibits *B. ammoniagenes* in vitro in dilutions of 1:200,000. Patch tests with 1:5000 dilution elicited no reactions. Of 50 cases treated, 49 were cured in a week, 1 case did not respond. There were 14 recurrences in two weeks after discontinuance of diapene, with a rapid response when it was used as a diaper rinse. These diapers should be a blessing to tired mothers. Diaper rash is a frequent occurrence and often resistant to treatment.

Robertson²¹ believes that the emotional background of a dermatitis may cause an acute exacerbation, and even resentment on the part of the patient. He presents a keen analysis of the patient's problems and the proper approach in directing their solution.

Forman²² reports that evipan narcosis offers a quick and probably reliable method of psychologic investigation that may be of value to the dermatologist for study on the basis of neurogenic cutaneous diseases.

MEDICAL PROGRESS

DERMATOLOGY

JOHN G. DOWNING, M.D.*

BOSTON

THE tremendous volume of papers on dermatology makes it impossible for the busy specialist to keep abreast of the literature. However, the establishment of the *International Abstract*, the *Quarterly Review of Dermatology and Syphilology* and the old favorite—the *Year Book of Dermatology and Syphilology*—lighten the burden. Many reports are repetitious, others are valueless. These reviews represent an attempt to separate the wheat from the chaff.

An excellent presentation of the skin manifestations of systemic disease has been written by Wiener,¹ who has coined the word "dermadrome" for such phenomena. The discovery of a systemic disease from a clue given by cutaneous lesions is very satisfying if the discovery prevents further extension of the disease, for example, the formation of small dark warty growths on the skin may lead to the early diagnosis of an operable intra-abdominal cancer, or bluish discoloration of the skin about the umbilicus may indicate rupture with an ectopic pregnancy.

In a study of the relation of acidity of the scalp to seborrhea, Cornbleet and Bergeim² found that the pH varied from 4.5 to 5.5, the acidity being chiefly due to lactic acid of sweat. Volatile acids were thought to be formed by the action of organisms on the lactic acid. These acids are believed to inhibit the growth of many micro-organisms and to cause itching when concentrated.

According to Lobitz and Mason,³ the palmar sweat glands, like the kidneys, seem able to form ammonia. Fifty-five specimens of sweat were collected from 5 normal men and 5 normal women and grouped in two physiologic types: profuse, 27 specimens, and intermittent, 28 specimens. Tests showed that the profuse palmar sweat had a lower concentration of ammonia nitrogen than the intermittent palmar sweat (7.7 and 28.9 mean, per 100 cc respectively).

In a comparison of sweat-gland response to direct heating and to reflex stimulation, Randall⁴ found that heat elicited profuse sweating by some glands, but the diffuse sweating that characterizes a reflex response was absent. There appears to be a threshold temperature, above which a direct response to local heat may occur and below which it does not occur. This critical temperature is several degrees above that necessary to induce sweating by reflex, when heat is applied to a large

area. Randall concludes that the profuse sweating response of individual glands to extreme temperatures is a direct one in contrast to the usual diffuse reflex response.

GENETICS

Whittle⁵ reports 2 cases of congenital poikiloderma, one in a twelve-year-old boy and the other in a four-year-old girl. There were areas of discoloration of the skin since birth, on the face, upper and lower extremities in one case and only on the cheeks in the other.

Acrokeratosis verruciformis (Hopf), a discrete keratoderma of the extremities, has a definite hereditary factor, as shown by Niedelman,⁶ who reports 4 males and 10 females of one family affected with this disease. Three males and 3 females in the same family were unaffected. This disease is differentiated from epidermodysplasia verruciformis, characterized by different types of verrucous lesions, by the fact that the histologic study reveals vacuolated cells in the latter. Niedelman questions whether this is sufficient to justify considering the diseases as different entities. He believes acrokeratosis verruciformis to be a hereditary nevroid dermatosis, possibly resulting from an inherited metabolic disturbance affecting normal utilization of vitamin A.

Porter et al.⁷ report 7 cases of Darier's disease (keratosis follicularis) in which 30,000 to 100,000 units of vitamin A were given daily for one to thirty months. There was great clinical improvement in 1 case, much improvement in another, little in 3 and no improvement in 2.

Hypertrichosis is frequently inherited. Reporting on electrolysis versus high-frequency currents in the treatment of hypertrichosis, Ellis⁸ states that electrolysis is slower but has less recurrences and rarely causes abscesses. Although the short-wave method is rapid, it has more recurrences and frequently causes abscesses and larger scars. Histologic study showed more severe damage to the epidermis resulted from diathermy, and most hairs recurred unless visible burns were produced, leaving scars. Destruction of the individual hairs either by electrolysis or high-frequency current is the only safe method of removing hair. I prefer electrolysis.

ENDOCRINES

Watson and Pearce⁹ chemically analyzed and tested against hyaluronidase biopsy specimens from 2 cases of pretibial myxedema and found that they

*Professor of dermatology and syphilology, Tufts College Medical School; professor of dermatology, Boston University School of Medicine.

demonstrated on isolated tissue or organs. The antagonism exerted peripherally could be modified by nervous or humoral influences in the intact animal.

A study was made of comparative anti-histaminic activity of six compounds by Winter.³⁵ He found that neoantergen caused fewer side reactions and that it was less toxic per effective dose than the other five compounds. Pyribenzamine was second in these qualities. Although these findings are claimed to be essentially in agreement with those of some investigators, they are at variance with others. Time will be required for proper evaluation of all these anti-histaminic drugs.

Halpern³⁶ did some experimental research on anti-histaminic drugs, thiopharylamine derivatives. Two derivatives designated "3015 R P" and "3277 R P" were reported to be less toxic and more active than the best previous anti-histaminic drug discovered by the French ("antergan").

Giving a detailed report on derivatives of N, N-dimethyl-N'-2-pyridyl-ethylenediamine as anti-histaminics, Litchfield and Adams³⁷ state that the substance was halogenated, producing two products tentatively named "chlorathen" and "bromathen," each of which is weight for weight twice as active and half as toxic acutely as pyribenzamine. Furthermore, it was noted that equal weights of either of these substances protect twice as long as pyribenzamine.

Henderson and Rose³⁸ report 64 per cent improvement in 138 allergic patients treated with pyribenzamine. Side effects in order of frequency were sleepiness, nervousness, nausea, dry mouth, vertigo, insomnia, headache and vomiting. Only 2 patients required discontinuance of the drug because of reactions. Pyribenzamine has been given for as long as a year without toxic effects. Its action, as well as that of benadryl, is temporary, and therefore a thorough search for the cause of allergy and its treatment remains necessary.

Urticaria due to sunlight is a distressing ailment. Ehrlich³⁹ showed by selective infiltration that the wave lengths of the offending rays lie between 3000 and 3750 Angström units. The patient was a thirty-five-year-old woman who for ten years had had urticaria on the areas exposed to sunlight. It is doubtful whether the positive transfer test in these cases is due to transfer of reagins (genuine allergy) or to a photosensitizing substance (a photodynamic phenomenon). Photosensitivity to sunlight from the use of sulfonamides is still an interesting problem. Watkinson and Hillis⁴⁰ report a study of a group of 470 soldiers receiving 2 gm of sulfanilamide daily for ten days as prophylaxis against epidemics of streptococcal sore throat. Vaccination for smallpox was given at the same time. Of 213 men receiving sulfanilamide after vaccination for smallpox, 49 per cent became photosensitive in one to ten days. These authors conclude that

the results support the hypothesis that drug reactions are due to liberation of toxins from a buried toxin focus, in these cases it was the vaccination with pustular stage that supplied the toxin.

Bradley⁴¹ reports a fatal case of periarteritis nodosa in a ten-year-old boy. The fact that this patient had had sulfonamides for otitis media at six years of age and was probably given the drug for three weeks prior to admission raises the question in her mind of the part played by sulfonamides and other drugs in the etiology of these diseases.

Rich and Gregory⁴² state that it is of interest that disseminated lupus erythematosus shows "sclerotic" coronary lesions of the same type as occur in rheumatic fever and periarteritis nodosa and in animals subjected to experimental serum sickness. These lesions, they state, must be related to lupus erythematosus, since they occur in children with that disease. Their work is well organized and controlled, and several good photographs support the statements.

In a report on erythema nodosum, Favour and Sosman⁴³ state that the concurrence of rheumatic fever and erythema nodosum is coincidental. However, both may be theoretically considered as hypersensitivity diseases. The multiplicity of unrelated infections and drugs known to initiate erythema nodosum has tended to obscure the role of the beta-hemolytic streptococcus. They state that mild secondary anemia, cervical adenopathy and occasionally enlarged hilar or bronchial lymph nodes characterized the illness, individual predisposition, a variety of infections and chemical agents and local trauma contributed to its occurrence.

Naide⁴⁴ gives an interesting discussion of allergic lesions following thrombophlebitis. Venous thrombosis may cause trapping of an allergen to bring out a subclinical allergic state or to accentuate a pre-existing allergic lesion, stasis dermatitis or eczema results. Trauma causes outpouring of these concentrated allergens into the area as demonstrated experimentally in a sensitized rabbit in which the traumatized ear became gangrenous after injection of the allergen, the noninjured ear being unaffected. This creates a vicious circle that causes chronic ulcers. Naide concludes by warning against the use of sensitizing drugs or even adhesive tape in these areas of stasis. Sensitizing drugs such as benzocaine, nupercaine, penicillin, mercury, resorcin and the nitrofurans should not be used in the treatment of a stasis dermatitis or eczema.

Reporting on intradermal tests with dirofilaria immitis extract in human filariasis, Zeligs⁴⁵ states that the test is of some value but that it cannot be depended on exclusively. It gives too many false-positive and false-negative readings to be dependable.

Young and Yeager⁴⁶ report 2 interesting cases of cyanosis secondary to the wearing of ink-stained athletic shirts. Two students practicing football

Owing to the ease of application, a new device, zippered elastic stockings, should be of value in the treatment of stasis dermatitides²³

Pfeiffer and Williams²⁴ think that a suspension of paraldehyde is a valuable sedative for patients suffering from pruritus. Its taste being obnoxious, it is disguised in the following prescription

SUBSTANCE	AMOUNT
Paraldehyde (U S P)	50
Powdered gum tragacanth	2
Glycyrrhiza syrup (as needed)	120
Make a suspension, shake before using 4 cc in ice water	

Combes²⁵ recommends a new tar preparation, zetar, but does not give its composition. Pure coal tar direct from the gasworks is an inexpensive and efficient preparation for the treatment of persistent cutaneous diseases. No matter how its derivative is incorporated in a compound, it helps a given number of patients, but sensitizes others.

Sharlit²⁶ does not believe that the alkalinity of toilet soap is dangerous for the skin. Nineteen samples of face powders bought at random were suspended overnight in water and the pH determined, all were on the alkaline side. He states that the fact that frequently used alkaline face powders do not cause damage to the face suggests that the damage from toilet soaps is exaggerated. He apparently disregards the difference in the methods of applying these substances.

Ellis²⁷ has reported 9 cases of allergic contact dermatitis due to wool fat and cholesterol.

By patch tests Lane and Blank²⁸ found that fatty acids of low molecular weight (lauric and oleic) were more irritating than those of high molecular weight. Among fatty acids present in soap in appreciable amounts, lauric and oleic acid gave more positive reactions. Patch tests of patients with chronic recurrent vesicular eruptions of the hands confirmed the foregoing observations. The authors state that sulfated oleic acid depends on the degree of sulfation for its irritation of the skin. If highly sulfated and combined with palmitic and stearic acids in a soap (dermolate), it is practically nonirritating.

I have followed with great interest the progress of the appearance of synthetic detergents during the last decade. The recent war, with its attendant shortages, gave them a tremendous impetus. The literature has been most misleading. Industrialists have installed expensive receptacles to supply these so-called nonirritant soap substitutes to the workers. Patients with erupted skins have been advised that they can use the detergents with impunity. It is my opinion that they are of little or no value and are much overrated, being promoted, as some brands of cigarettes are, through a few well chosen papers by nonmedical research

workers supported by grants given to large clinics. I have tested them on normal and diseased skins and found them wanting. I prefer the soaps from natural oils for normal skins and soothing vegetable oils for inflamed skins.

Apparently there will always be a skin perverse enough to do the unexpected—for example, to become sensitized to an anti-histamine drug. A case is reported of an eczematoid dermatitis of the hands, chest and thighs appearing after the use of pyribenzamine to prevent recurrent colds. With cessation of the dermatitis, repetition of ingestion of the drug caused a recurrence²⁹. This type of reaction challenges the histamine-release theory of allergic dermatoses.

Lowell³⁰ states that the understanding of allergic reactions remains incomplete. The difficulty lies in the absence of a direct means of investigating the conditions. Apparently it is the cell itself that is sensitized, and this is why these drugs have been of so little value in contact dermatitides.

Whittemore and DeGora³¹ report a successful passive transfer to sulfadiazine twenty-five days after an acute episode. Ten minutes after a dose of 0.5 gm of the drug (which had been taken a month previously for treatment of furunculosis), the patient had a cutaneous reaction consisting of itching, flushing and large wheals.

Frazier and Small³² present a thorough consideration of the immunologic and biochemical implications of allergic dermatitis. Their rational and inquiring discussion covers the question whether drug reactions are due to sensitization or toxicity and operate directly or by tissue combination. The authors believe that the disturbance in lipid metabolism that occurs in this disease should be investigated.

Aminophyllin (0.5 gm in 20 cc of fluid given intramuscularly) was tried by Epstein³³ in 17 cases of pruritic eruptions. Seven patients had dramatic relief in three to forty-five minutes, with no recurrence for twelve to thirty-six hours. One patient with eczema obtained relief for six days. Two patients were relieved, and subsequent injections controlled recurrences. Three patients with eczema, 2 with generalized pruritus and 1 with urticaria experienced no relief. Three patients obtained mild benefit, and 1 failed to return. It was noted that the local and general reactions were too severe for general use of this drug as an anti-pruritic agent. The injections require care in preparation, are very painful, with soreness persisting for days, and cause nausea. One patient nearly died from shock, and another menstruated for fifteen minutes after each of six injections. In this therapy, the cure is worse than the disease.

Loew³⁴ states that the major action of anti-histamine drugs is probably exerted directly on the peripheral effector cells that respond to histamine, since antagonism has frequently been

Occupational cutaneous cancer in England is discussed by Henry⁵⁶ in a detailed statistical report that describes the nature of the cancer's beginning, sites of predilection and progress. Workmen's compensation for epitheliomas in chimneysweeps or workers in pitch, tar or tarry compounds was first allowed in 1907. In 1914 it was enlarged to include cancer from mineral oil, bitumen and paraffin or their derivatives. Cancer resulting from arsenic has been a notifiable disease since 1896.

Schwartz⁵⁷ describes occupational pigmentary changes in the skin. They consist of excess of melanin and melanoid, metallic substances deposited in the skin (tattooing) and staining from external or ingested dye. Occupational causes of unusual formation of pigment in the skin are excessive exposures to actinic rays, coal tar, crude petroleum and residues of distillation, and asphalt. The last three are photosensitizers. Depigmentation results from injuries, from skin infections and from monobenzyl ether of hydroquinone, the anti-oxidant in rubber manufacture. The last is the only chemical reported to have caused occupational depigmentation without causing dermatitis. The action is not entirely clear.

According to Klauder and Brill,⁵⁸ the irritant action of petroleum solvents, like the defatting action, decreases as the boiling range increases. Petroleum solvents with boiling ranges up to and including that of kerosene are primary irritants. Beyond kerosene there is varying reaction from none to positive. In this report Negroes had the highest tolerance. Patients with dermatoses due to petroleum solvents had less tolerance than patients with those from other causes. Naphthenic kerosene gave more severe reactions than paraffinic kerosene of the same boiling point. Klauder and Brill conclude that petroleum-solvent dermatitis is a nonspecific sensitivity.

METABOLISM

In a paper on acne rosacea, Tulipan⁵⁹ states that telangiectasia, erythema, papules, pustules and hypertrophy are probably due to a deficiency of vitamin B complex, as a result of lack of intake or by faulty absorption. He cites a series of 96 cases whose response to treatment indicated that this deficiency is the primary cause of rosacea. Local treatment included an antiseptic and the following hydrophilic ointment:

SUBSTANCE	AMOUNT
Red oxide of mercury	0.075
Sulfur precipitate	15
Salicylic acid	10
"Quinolol compound ointment"	20
Aquaphor (as needed)	300

In my experience, local therapy with antiseptic compounds is a necessary adjunct to the internal

treatment of rosacea. Endocrine therapy in women seems to be of value.

Sachs et al.⁶⁰ give a brief but clear presentation of their ideas on a confusing dermatologic entity frequently mistaken for dermatophytosis, even by dermatologists. They suggest the name "acrodermatitis pustulosa perstans." Their report of 11 cases states that the eruption clinically may be identical with pustular bacterioid or pustular psoriasis. It persists for years and seldom remits entirely, beginning as a vesicle or pustule (sterile) on the palms, digits or soles, with predilection for the thenar portion of the palms and the center of the soles extending to the inner side of the feet. Treatment generally is ineffective. Occasionally, removal of a focus of infection or the internal administration of arsenic produces a cure.

Caro and Seneor⁶¹ consider a nonpustular psoriasis of the hands (with or without psoriasis elsewhere) to be more frequent than is generally believed. These lesions, usually seen on the extensors of the finger joints and knuckles, sides of the fingers, palms and fingertips, are bilateral but not always symmetric. A biopsy is often necessary for diagnosis. These cases are frequently mistaken for occupational eruptions.

Brunsting and Mason⁶² report further studies on porphyria, stating that pigmentation occurs in the acute form but that other cutaneous reactions are rare. In congenital porphyria, however, there is marked sensitivity to light, and in the chronic disease there are bullous eruptions after light exposure and the skin reacts to trauma in a manner similar to epidermolysis bullosa.

Dunsky et al.⁶³ report a normal-appearing newborn baby who at two months began to pass red urine. This continued, and the patient presented loss of fingernails and bullous lesions of the hand that resisted treatment, healing with pigmented scars. The teeth were purple brown, and there was pronounced generalized hypertrichosis. Splenomegaly occurred, and the skin became more fragile. The authors include a thorough report of the chemical study of the porphyrins.

Eosinophilic granuloma, despite its rarity, is still a popular subject for theoretical discussion. Thannhauser⁶⁴ believes that this entity is only a stage in a large syndrome, which might be entitled eosinophilic xanthomatous granuloma.

In a discussion of the syndrome of "burning feet" as a manifestation of nutritional deficiency, Glusman⁶⁵ states that burning feet were first described and attributed to dietary deficiency by the British in Burma in 1826. American prisoners in the Philippines from 1942 to 1945 were afflicted by the thousands, with or without other symptoms. The first symptoms were numbness, tingling and burning of the toes and soles. Later there were sharp shooting pains in the legs, usually bilateral and worse at night. In some severe cases there was

wore sweaters heavily numbered with Sanford's indelible ink, containing carbon black, phenol, ammonia, nigrozone and aniline oil. They developed generalized cyanosis with nervousness, vertigo and dyspnea, the symptoms subsiding in approximately twelve hours. In conclusion the authors state that indelible ink containing aniline oil will produce methemoglobinemia if allowed to remain in contact with the skin for a sufficient time.

A severe delayed reaction to penicillin is reported by Dolan.⁴⁷ The patient, a twenty-six-year-old man, gave a history of treatment with penicillin intramuscularly three years and two months previously. The ear canal was treated with penicillin, both orally and locally. Three days after treatment generalized pruritus and raised, erythematous areas, 1 to 6 cm in diameter, developed. Three days later the condition progressed to frank edema about the face and scalp, pitting edema of the ankles and feet, soreness of the buccal mucous membranes and pains in the muscles of the abdomen, back and extremities, with a temperature of 100.2°F.

Hopkins and Lawrence⁴⁸ state that sensitization from the local application of penicillin is not sufficient to prevent its subsequent parenteral use. They found sensitization severe enough to prevent or prohibit systemic treatment in less than 1 per cent of the cases.

Templeton et al.⁴⁹ state that penicillin contains two antigens—penicillin and its culture medium. Types of dermal reactions have been toxic, macular or scarlatiniform, occurring in the first few days after penicillin therapy was started, urticaria (most frequent and occurring seven to nine days after penicillin) and erythema multiforme and nodosum, bullous and lichenoid, which may occur a few hours after penicillin injection. Circulating antibodies were believed to occur on the basis of a modified Prausnitz-Küstner reaction.

According to Kiel,⁵⁰ pyoderma gangrenosum (ulceroneurotic skin lesions) and possibly the associated ulcerative colitis may be allergic reactions to bacterial infection elsewhere. She reports the case of a thirty-eight-year-old woman with an acute to chronic colitis of three years' duration, who suddenly developed many rapidly spreading, roughly symmetrical ulcers on the extremities and torso, with fever, hypoproteinemia and bone-marrow depression.

When gold compounds were injected in lethal doses into rats, BAL increased the survival time for all compounds studied—gold sodium thiosulfate, thioglucose and sodium succinidoaurate—with the exception of gold sodium thiomalate.⁵¹ In 2 cases observed BAL produced rapid amelioration of the acute signs of a dermatitis due to gold, but final healing of the eruption followed the usual course of a slow return of the skin to normalcy.

Application of the following prescription prior to exposure was successful in the prevention of mustard-gas burns.⁵²

SUBSTANCE	AMOUNT
Glycerol	50
Chloramine-T	18
Zinc oxide	50

Aldrich⁵³ treated 54 cases of pruritus ani and vulvae with undecylenic acid (2 per cent) in triethanolamine and zinc stearate in a water-miscible base—an emulsion. Fifty (88 per cent) were cured—that is, with no recurrences to the time of his report—in four to thirty-three days by the local application of this emulsion. Four cases were complete failures. Any such report needs confirmation. My experience in the treatment of pruritus ani and vulvae is at times disheartening.

OCCUPATIONAL DISEASES

Benedek⁵⁴ presents a differentiation between pompholyx and occupational dermatitis to remove confusion regarding the diagnosis and treatment of the latter. He claims that in 1925 he discovered *Bacillus endoparasiticus* to be the cause of pompholyx, and that this organism is constantly harbored in a location as yet unknown, frequently in the blood. It is his contention that if one gets a contact dermatitis at this time, the organism causes pompholyx in the injured skin, and cure is difficult or impossible without the use of an anti-endoparasitic vaccine. His ideas are in conflict with the present generally accepted concepts.

Hanzlik⁵⁵ studied the epidermal application of diethylene glycol monoethyl ether (carbitol). Carbitol and other glycols were rubbed on the skin of rabbits, in aqueous form or in ointment bases. Renal and liver damage (necrosis) were observed with toxic dosage, and this led to death. The order of toxicity was as follows: diethylene glycol was more toxic than ethylene glycol, technical carbitol, ethylene glycol and propylene glycol were more toxic than carbitol, and the LD₅₀ of carbitol was 0.32 cc to 0.08 cc per kilogram of body weight daily. The safe dosage is probably 0.04 to 0.02 cc per kilogram of body weight a day. Hanzlik's paper is a thorough investigation of a cosmetic and its industrial preparation. According to the Pure Food and Drug Administration, "any amount in excess of 5 per cent in preparations for topical application to small areas of the body would constitute a hazard." This study is of extreme value because of the use of carbitol and glycol in the formulas of various solutions and ointments containing medication. This toxicity must be considered when large amounts are used in large ulcers and sinuses over a long period.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 35081

PRESENTATION OF CASE

First admission A twenty-five-year-old single laborer entered the hospital because of varicose veins.

The patient was first seen in the Out-Patient Department three years previously for intermittent pain in both legs, occasionally associated with swelling. During the next three years he experienced occasional cramps in the legs and developed small, chronic, 1-cm ulcers above the medial malleoli. Physical examination was otherwise negative. A bilateral, long saphenous ligation was performed. The ulcers healed readily but about two months later reappeared.

Second admission He re-entered the hospital, where venograms indicated a blockage of the deep system. A bilateral lumbar sympathectomy was performed and dermatome grafts applied following excision of the leg ulcers. Positive blood Hinton and Wassermann tests were discovered, and he was discharged to the Out-Patient Department for treatment with mercurials and bismuth. The spinal-fluid serologic findings were negative. During the mercurial therapy he developed jaundice and albuminuria, and mercury was temporarily discontinued.

Third admission (five years later) During the interval the patient was seen periodically in the Out-Patient Department. The leg ulcers persisted without much change. The symptoms were improved, although he did not return to work. The day before this admission he had a hemoptysis (a cupful of bright-red blood). Physical examination revealed a nasal septal defect, distended pulsating neck veins, an enlarged heart, with a prolonged rough apical systolic murmur and accentuated pulmonic second sound, and generalized edema, particularly in the legs. The blood pressure was 110 systolic, 75 diastolic. A blood Hinton test was negative. The venous pressure was equivalent to 320 mm of water. The blood and urine examinations were negative. An x-ray film showed a heart enlarged in all directions. There was prominence of the pulmonary conus. The main branches of

the pulmonary artery were likewise dilated. There was no evidence of pleural fluid. The lung fields were not remarkable except for the dilated blood vessels. Fluoroscopy showed marked pulsation of the main pulmonary artery, but little pulsation of the hilar shadows. There was no enlargement of the left auricle; the aortic knob was almost absent.

An electrocardiogram showed right-axis deviation with evidence of right ventricular strain. The patient remained in the hospital about two months on a low-sodium diet, ammonium chloride and digitalis, during which he had a good diuresis. He had some paranoid and hallucinatory episodes.

Fourth admission (two and a half months later) He re-entered the hospital because of gradually increasing dyspnea and edema. In addition to the previous physical findings there was anasarca, a slightly enlarged liver and ascites. He remained in the hospital for three weeks under digitalis, mercupurin and urea treatment. The total serum protein varied between 5 and 6 gm per 100 cc, and the nonprotein nitrogen ranged from 25 to 60 mg per 100 cc.

Fifth admission (six months later) He was re-admitted to the hospital because of an episode of hemoptysis. At this time he had massive edema. X-ray examination showed no evidence of intrapulmonary hemorrhage. Findings in the chest were much the same as those on last examination except for the transverse diameter of the heart, which was now 18 cm compared to 17 cm six months previously. An electrocardiogram showed auriculoventricular block, with findings consistent with chronic cor pulmonale.

Sixth admission (two years later) He was followed in the Out-Patient Department, with occasional exacerbation of the edema and treatment of the persistent leg ulcers. He re-entered the hospital with edema, more pronounced dyspnea, and complaining of yellow spots before his eyes. An electrocardiogram showed right-axis deviation and bigeminy. Digitalis was withheld temporarily, with disappearance of the bigeminy and the usual symptoms. During his hospitalization he exhibited several acute psychotic episodes with paranoid delusions. The total protein was 4.1 gm, and the nonprotein nitrogen 42 mg per 100 cc.

Seventh admission (four months later) At this admission he exhibited marked generalized edema. The total serum protein was 3.94 gm per 100 cc, with an albumin-globulin ratio of 1.1. The sodium was 129.9 milliequiv, the chloride 92 milliequiv, and the carbon dioxide 22.3 milliequiv per liter, the nonprotein nitrogen was 42 mg per 100 cc. An x-ray examination showed the heart to be slightly larger than on the previous examination, and there was definite evidence of fluid in each pleural cavity (Fig. 1). Some pulmonary edema was present, particularly in the left-upper-lung

involvement of the palms Many patients had pelagra rashes, scrotal dermatitis, fissuring at the angles of the mouth, edema, diarrhea and so forth These responded to nicotinic acid and riboflavin or B complex, whereas the burning feet persisted

Lloyd and Williams⁶⁶ report a study of endocrine function in 71 patients with cirrhosis of the liver Clinical endocrine changes observed in male patients consisted of decreased libido and potency, atrophy of the testicles, decreased body hair and gynecomastia Telangiectasia and "liver palms" were also regarded as possibly being related to altered endocrine function Decreased axillary hair was present in 46 of the 55 male patients (84 per cent)

An editorial in the *Journal of the American Medical Association*⁶⁷ states that "until clinical studies have been reported and critically analyzed, the local use of amino acids to accelerate wound healing can be considered only as an interesting observation "

(To be concluded)

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the written report, especially as regards the density of the lung roots Dr Wyman, would you discuss the films?

DR STANLEY M WYMAN As I understand from the record, these films begin and end in the last two-year period of the patient's illness and do not include the first admission. The most striking feature of the original examination is the markedly enlarged heart, the enlargement being more impressive toward the right than toward the left. In addition to that there was a very large main pulmonary artery. The aortic-knob shadow is lost in this region. I cannot identify it with certainty on any film so that it must be at most of normal caliber if not small. The vascular shadows extending into the lung at the right hilus are definitely more prominent than usual, and on the left there is still greater enlargement of the main branches. This prominence of the vascular pattern extends into the lung field, and I think possibly it is a little more pronounced in the left lung than in the right. I believe that the patient had on first admission a very small quantity of fluid in the right pleural space. The record in the X-ray Department stated that pulsations of the cardiac borders were of good amplitude, slow and regular. They described increased prominence of the amplitude of pulsation of the main pulmonary artery, but no hilar dance. They do not say whether or not absence of pulsations of the hilar arteries was ever observed. I think the lateral view shows the heart extending far upward along the sternal border, suggesting right ventricular enlargement, and there is a high pulmonary artery here arching in this fashion and in back of the main pulmonary artery a branch that is very large. There is just the faintest suggestion of the aortic arch above the pulmonary artery. As Dr Bland has pointed out, we did not think that the left auricle was enlarged.

The right anterior oblique view shows the trachea and the bifurcation of the main bronchi with a definite compression of the left main bronchus about 4 cm beyond its origin. I take this process to be due to unusual enlargement of the left main branch of the pulmonary artery. I cannot outline the diameter because I cannot separate it from the other overlying shadows. The other examinations were taken subsequently — these films were a year and four months after the original films and show the heart to be slightly larger and the vascular engorgement, if anything, to be slightly more pronounced. I agree with Dr Bland that I cannot be sure of the pulmonary edema described at one point in the left-upper-lung field. The film taken two years after the original films shows still further cardiac enlargement, and I think that the left hilar vascular shadow is increased still further and perhaps out of proportion to the increase in the right. There is a knob of density on the right just above the right main bronchus, which I believe is the

azygos vein. The best I can say on this is that the heart is enlarged, probably chiefly right ventricular and right auricular, with a huge main pulmonary artery and branches, particularly the left hilar branches, which seem to have increased in size out of proportion to the right.

DR BLAND I would like to know the extent of pulsation in these hilar vessels beyond the main stems.

DR WYMAN I do not know that.

DR BLAND The implication is that it was present but not striking.

DR WYMAN It certainly was not increased.

DR BLAND You do not find evidence of old or recent infarcts?

DR WYMAN No, we looked particularly for infarcts and we were unable to see any clear-cut evidence.

DR BLAND This man bled a fair amount on several occasions. There was a statement in the record that there was no x-ray evidence of intrapulmonary bleeding. I cannot quite follow that.

DR WYMAN I do not believe that by x-ray study one can say that a lesion in the lung is hemorrhagic unless asked a specific question and there is a good history to go with it. In the past we have seen hemorrhage lying peripherally in the lung field in a large circumscribed area, not having the distribution of infarct and having a homogeneous character with borders of poor definition. When lesions of this character have cleared up promptly we have assumed them to be hemorrhage. One such case discussed at one of these conferences perhaps a year ago, but not published, actually was removed surgically and proved to be hemorrhage.

DR BLAND So the point is that you do not see anything that suggests a hematoma in the lung?

DR WYMAN No.

DR BLAND The first possibility that occurred to me in reading through the record was auricular septal defect. After seeing the films I am willing to discard that for several reasons. With auricular septal defect a tremendous volume of blood circulates around and around through the pulmonary system, and by cardiac catheterization it has been shown that the cardiac output with this defect is tremendous, at times up to 25 or 30 liters of blood, with only 3 or 4 liters going to the periphery. That indicates a great amount of blood circulating through the lungs. Under these circumstances the lung roots are massive. Therefore, I think we can safely discard that possibility after viewing the films.

What other congenital lesions should we consider that are noncyanotic at birth and yet may become slightly cyanotic later? One is the so-called Eisenmenger's complex, which is a modification of the tetralogy of Fallot. In this condition cyanosis usually appears in adolescence, and later with heart failure the patients are apt to be extremely blue. This does not quite fit the picture here. I cannot

field. He was discharged after about two weeks and remained at home for three weeks.

Final admission He was admitted finally with generalized anasarca and gangrene of the right third and fourth toes.

He had loss of memory for recent events. There was pronounced venous distention in the neck. Both lung bases showed dullness to flatness, with diminished breath sounds and fine, moist crackles. The left cardiac border was percussed 3 cm. to the left of the midclavicular line. A Grade IV harsh systolic murmur was present, most marked near the apex. The pulmonic second sound was greater than

It is always annoying for the discussor to ask for something that is not available, and I am sure some one has spent many hours abstracting this long record, but before I start I really ought to know whether or not this man was cyanotic.

DR J H MEANS Yes, he was.

DR MORTON SWARTZ No, he was not cyanotic. That was one of the striking features.

DR TRACY B MALLORY There seems to be a discrepancy, but I think it varied on different entries. There are a number of comments that he was not cyanotic, and others that he was.

DR MEANS I would swear that I had seen him when he was at least somewhat cyanotic.

DR BLAND The original red-cell count might help.

DR MALLORY On the first admission there was a single red-cell count of 6,500,000, followed within a week by a count of 5,100,000 and one of 4,800,000. All subsequent counts were within normal range.

DR BLAND In any event we must explain this patient's pulmonary hypertension. The evidence is quite clear that that existed to an extreme degree. His main pulmonary artery was large and pulsating. He had a loud pulmonic second sound, and the heart failure was limited to the right side. Mitral stenosis is the commonest cause of pulmonary hypertension. He did not have mitral stenosis for several reasons. The lungs remained uncongested throughout his illness. This much heart failure secondary to mitral stenosis without congestion of the lungs could not exist. I question the statement of slight pulmonary edema on one occasion. There was no intracardiac calcification. That is not always present, however, with mitral stenosis. He had two years of heart failure and did not fibrillate. That would be most unusual if there were an important element of mitral stenosis. Besides, the X-ray Department said that the left auricle was not large. They make mistakes on that score, but nevertheless, I am certain that his pulmonary hypertension and heart failure were not due to rheumatic heart disease and mitral stenosis.

We are left with two broad possibilities. He had either some congenital lesion of the heart, which increased the amount of blood flow through the lungs, or something in the lungs in the pulmonary vascular bed, which gave him pulmonary hypertension. This morning I was told that it was all right to look at the x-ray films with the X-ray Department, and I urgently needed their help in this connection, especially to differentiate congenital defect from obstruction in the pulmonary circuit.

As to the presence of cyanosis, different opinions have been expressed. Most people with heart failure get a little dusky at times, but I think it is safe to assume that this patient was not constantly cyanotic. In viewing the films I was left with a different impression from that obtained from



FIGURE 1

the aortic second sound. The abdomen was tense, with pitting edema of the abdomen, flank dullness and a fluid wave.

The blood pressure was 110 systolic, 70 diastolic. Examination of the blood showed a hemoglobin of 10 gm. and a white-cell count of 17,650, with 90 per cent neutrophils.

Following admission the patient became more disoriented and had a hemoptysis (about 150 cc of bright-red blood). Although transferred to a psychiatric ward, his management became so difficult that transfer to a state sanatorium was necessary after about ten days.

He died about five days following the transfer.

DIFFERENTIAL DIAGNOSIS

DR EDWARD F BLAND When Dr Castleman asked me to discuss this case he said that I must have seen this patient at some time. He said that did not matter, however, the implication was evident. He even offered to let me abstract the record, but I thought that that might be too confusing so I did not do that. I have studied the x-ray films, however, with the X-ray Department.

DR BLAND That always comes up, and it is hard to answer. I do not know of any relation between the two. Do you, Dr Mallory?

DR MALLORY Buerger's disease has been claimed to involve the lungs. I do not know the evidence, however, and I have never seen it myself.

DR BLAND I think we can discard syphilis without serious thought.

DR WYMAN I wonder if Dr Bland attaches any significance to the apparent discrepancy in size of the two main hilar branches of the pulmonary artery.

DR BLAND That was fairly striking and is suggestive of unilateral thrombosis.

DR WYMAN The larger left hilar shadow is associated with apparently larger vessels throughout the left lung. It is very disturbing to make a diagnosis of thrombosis in the main pulmonary artery.

DR BLAND Unless it happened at this point (on the film).

DR WYMAN Yes, in back, and you cannot see it.

DR BLAND Is it fair to give Dr King a chance since this involves the lungs?

DR KING I had a similar case a year ago with phlebitis and varicose ulcers and cor pulmonale, and my guess was emboli, multiple small pulmonary emboli. I was wrong, it was primary vascular disease, so my inclinations here would be to make this primary chronic pulmonary vascular disease, as you have done.

DR MEANS Can I ask Dr King what kind of chronic pulmonary vascular disease?

DR KING I think it was called arteriosclerosis, if I remember correctly.

DR BLAND Dr Wyman wants to put a thrombus in the main right-pulmonary-artery stem behind the heart where it cannot be seen.

CLINICAL DIAGNOSIS

Cor pulmonale, cause undetermined

DR BLAND'S DIAGNOSES

Obliterative pulmonary-artery disease

Cor pulmonale

Congestive failure

Peripheral vascular disease (venous and arterial)

ANATOMICAL DIAGNOSES

Embolism and thrombosis of pulmonary-artery tree, diffuse, with organization and recanalization.

Cor pulmonale

Thromboangitis obliterans, leg vessels?

Ascites

Operative wound, old, lumbar sympathectomy, bilateral

PATHOLOGICAL DISCUSSION

DR MALLORY Autopsy showed a large thrombus in the main pulmonary artery, beginning 3 cm distal to the valve. It then extended to the bifurca-

tion and spread into both hilar arteries, completely occluding the one on the left and only partially occluding the one on the right. The cut surfaces of the lung parenchyma showed that all the vessels throughout both lungs were prominent and stiff and stood out from the surface. In many of them it was quite evident that the lumen had been at one time obliterated since small canalizing vessels were present within the larger ones. This process extended down to the most minute vessels in the lung.

In the upper right-hand corner of the microscopical slide can be seen a vessel that has been divided in two by a band of fibrous tissue, with two canalizing vessels on each side. In this next field is a vessel that has been divided into half a dozen different lumens by multiple fibrous septums. Here is a vessel with very marked intimal thickening and a single lumen, very much hypertrophied. Here are several extensively recanalized small vessels.

One is still left with the question of etiology of this process. It involves pulmonary arteries of all sizes from the main pulmonary artery down to the smallest arterioles—fairly uniformly distributed throughout both lungs. The changes all seem to be internal to the internal elastic lamina, there are no changes in the media of the vessels. They can all be explained on the basis of multiple pulmonary emboli with organization and recanalization, followed by a retrograde thrombosis going back into the main arteries. I do not see any way that I can prove that is the case. It is not very different from what has been described as primary endarteritis except that the multiplicity of the canalizing vessels is much more like organization of emboli.

DR GORDON S MYERS Was any source for emboli found?

DR MALLORY There was extensive disease of both arteries and veins in the legs, with almost complete obliteration of the left femoral artery about 6 cm below Poupert's ligament. None of the changes at the time of autopsy were characteristic of Buerger's disease, and the original biopsy, to my eye, was not characteristic either. The biopsy showed a large vein, which looked like a recanalized varicose vein and not particularly like Buerger's disease. But Buerger's disease is only specific in its histology for a brief period in the acute stages. In later, chronic stages one can only guess about it.

DR MYERS Did this disease involve the capillaries as well as the arterioles?

DR MALLORY It went as far as the smallest arterioles, but no capillaries were involved that I could make out.

DR MEANS If there was an embolus large enough to shut off one main branch of the pulmonary artery, would it not have been suddenly fatal?

DR MALLORY I suppose so.

DR MEANS If due to embolism, we must assume small ones and subsequent retrograde thrombosis.

think of any other congenital derangement that we need consider seriously. Another remote possibility is arteriovenous fistula in the lung, which we now and then see producing strain on the right side of the heart. It is usually evident by x-ray study and is apt to produce bruits.

I am forced back for a diagnosis to the pulmonary vascular bed itself — either primary or secondary obliterative disease of the pulmonary arterial tree. One possibility is pulmonary obstruction secondary to chronic lung disease. This man gave no history of chronic pulmonary disease. He never coughed, wheezed or raised significant sputum, and there was no evidence to suggest it by x-ray study. Of course, extensive lung fibrosis with cor pulmonale can exist without much x-ray evidence in the lung itself. Is that true, Dr Wyman?

DR WYMAN Absolutely true.

DR BLAND Can it exist to that degree, Dr King, without symptoms pointing to pulmonary disease in the way of cough, wheeze or sputum?

DR DONALD S KING Almost never.

DR BLAND This patient had no lung disease. Therefore, we are left with the pulmonary arterial bed as the likely cause of his trouble. We have studied here, and Dr Castleman is now in the process of reviewing pathologically, about 12 patients with so-called primary disease of the vascular bed itself involving a variety of processes but most often an obliterative endarteritis of the smaller vessels and of unknown etiology. We have seen it in an infant a few months of age. In most cases in which we have puzzled over the cause of cor pulmonale and have not been able to identify a congenital lesion of the heart or chronic disease of the lungs, our experience has been that it usually turns out to be pulmonary endarteritis, unexplained. I am betting heavily on that possibility here. In some of the cases we are reviewing, the changes in the pulmonary vessels are secondary to showers of small emboli. Dr Castleman and I¹ reported a case two years ago of a patient we had observed clinically for eight years with a large heart and right-sided failure. The vascular system in the lungs was different from any of the others. The obstruction was limited throughout both lungs to the tertiary vessels, and some had recanalized. Elsewhere in the vascular tree there was no obstruction. The lungs were all right. We could not explain this widespread uniformly localized obstruction except that at some time or other there had been showers of emboli, all of about the same size, that had plugged these tertiary vessels throughout the lungs. There has been an occasional patient who, secondary to disease elsewhere in the body, has developed secondary thrombi in situ in the main pulmonary stems. Drs Means and Mallory² long ago reported such a case in which there was thrombosis and obstruction of the main pulmonary trunk. A few

months ago a case was discussed here in which the X-ray Department had cleverly pointed out two large pulmonary stems, one of which pulsed vigorously and was accompanied by increased vascular roots all the way out in the lung, whereas the other pulsed for a short distance and the lung was relatively avascular beyond that point. It was suggested that there must be a local pulmonary thrombus in that main vessel, and this proved to be true at autopsy. Our patient today had serious peripheral vascular disease, both arterial and venous, and had had episodes of bleeding in the lungs. The interpretation of these episodes has bothered me somewhat since with primary arterial disease in the lungs there is usually no bleeding. Actually, the blood does not adequately get to the lungs. It is pulmonary ischemia. They may or may not be cyanotic.

In conclusion I think this patient had obliterative vascular disease of the lungs. Furthermore, I believe it must have been primarily of the small vessels rather than of the large pulmonary trunks.

DR MEANS I saw this man on several admissions, and my recollection of this case is fairly vivid. But I am a little let down because I cannot find on studying the record a statement that he was cyanotic, although I have a vivid recollection that on the last admission he was somewhat cyanotic. To make a long story short, everyone knew that he had some sort of cor pulmonale, but what kind was the question. A note made by Dr Wheeler in 1945 is worth reading. "The Cardiac Group believes that this patient has chronic cor pulmonale, probably on the basis of pulmonary arterial obliterative disease. Constrictive pericarditis seems to be well ruled out by the x-ray and electrocardiographic findings, so that exploration of the heart does not seem advisable." We did not get any further than that. On several subsequent admissions he had cor pulmonale and chronic insufficiency, and no one knew beyond that just what the situation was. I wrote last November in the record "As far as I can make out the fundamental nature of this cardiopathy remains a mystery. Cor pulmonale, yes, but due to what? I would still cling to the possibility of pulmonary-artery thrombosis. He has tight ascites, which diuretics no longer relieve completely. I see no objection to an abdominal tap as symptomatic treatment." That is all I contributed to this situation. We might later come back to the case Dr Bland mentioned.

DR BLAND I assume that this patient's heart was not catheterized? That would have excluded a shunt.

DR MALLORY It was considered and believed to be too dangerous.

DR HAROLD E ELRICH He had Buerger's disease of the leg. Do you think there is any tie-up between pulmonary-artery disease and that?

obstruction due to adhesions of the small intestine I think it is unlikely in this particular patient, but it is something one should always think of when one sees a scar on the abdomen with an acute abdominal condition.

The physical examination was essentially negative, I think, except for the fact that she had diffuse abdominal tenderness, most marked in the right lower quadrant and epigastrium. It is of significance that the temperature was normal—98.6°F. I presume that is to be relied upon and, if so, rules out the question of peritonitis at the time that she was admitted so that I doubt that she had a condition at that time that was producing peritonitis. The cardiovascular system was in a satisfactory condition for her age. The blood pressure was 175 systolic, 80 diastolic. She had not lost much blood, since the hemoglobin was 14 gm, unless she was dehydrated, which can elevate the hemoglobin. We have no other figure on the hemoglobin so if she was bleeding, I will have to leave that to Dr. Mallory to tell us about.

The serum amylase was 45 units per 100 cc. I believe in our laboratory the normal is somewhere in the vicinity of 30 units, is that right, Dr. Mallory?

DR. TRACY B. MALLORY: Yes.

DR. LINTON: The serum amylase was slightly elevated. Undoubtedly those taking care of her were thinking of acute pancreatitis, which one should consider in a patient complaining of epigastric pain and the other associated symptoms. I would say that 45 units of serum amylase was equivocal, it does not help one way or the other in making a diagnosis of pancreatitis. If she had pancreatitis beginning four weeks before admission, one would expect a normal serum amylase after that long a period. As a matter of fact, the determination usually returns to normal fairly promptly when an acute pancreatitis develops—I think within a matter of forty-eight hours. The other point regarding serum amylase is that it is a test that cannot be relied on too much to make a diagnosis of pancreatitis because there are other acute abdominal conditions, even biliary-tract disease, that give an elevation, as I believe this patient demonstrates, although the elevation was not very marked.

The nonprotein nitrogen was normal. From the surgical point of view the x-ray films are of interest in any patient who has an acute abdominal condition in which one suspects intestinal obstruction, and I think one would suspect it in this case.

DR. STANLEY M. WYMAN: The posteroanterior film of the chest shows the lung fields grossly clear. The heart shadow is not remarkable for a woman of this age. There is no evidence of gas beneath either leaf of the diaphragm. The liver shadow and the spleen do not appear unusual. The lateral view of the chest shows an increase in the anteroposterior diameter, I believe, in keeping with the patient's given age. Plain films of the abdomen

show again that the liver is grossly normal, and the spleen not enlarged. This one loop of gas-filled bowel certainly suggests small bowel, probably jejunum, and it is wider than usual, but I think it is insufficient evidence to make a flat-footed diagnosis of intestinal obstruction. I believe the small, round shadow of calcification described may possibly lie in cartilage. The bones are osteoporotic but show no definite destruction. I cannot identify any unusual soft-tissue masses.

DR. LINTON: A plain abdominal film in a patient whom one suspects of having intestinal obstruction is an extremely important diagnostic aid because by means of it one can frequently detect early intestinal obstruction and certainly can readily detect an advanced intestinal obstruction. My opinion on looking at these x-ray films and listening to Dr. Wyman's description of them is that this patient obviously did not have intestinal obstruction of sufficient degree to explain the nausea and vomiting—as well as the fact that she had diarrhea, which would be hard to connect with intestinal obstruction. The x-ray film on the left shows even less gas than one usually sees in a plain abdominal film. Do you agree?

DR. WYMAN: That is true. On the far right there is a little gas in the colon and in the one loop that represents presumable jejunum.

DR. LINTON: I feel quite sure then that we can rule out intestinal obstruction as the cause of her symptoms. The white-cell count twelve hours after admission was 22,000, indicating some pathologic process sufficient to increase the count which, as a matter of fact, increased from 16,000 to 22,000. Of extreme significance, I think, is the fact that the blood pressure dropped to 125 systolic, 70 diastolic, and that the pulse rose to 160. Something was going on within the abdomen that had produced these changes, which apparently had been rather dramatic as they came on within twelve hours of admission. Associated with that she had the terrific bouts of pain that made her writhe about. Her condition did not improve. The peristaltic sounds in the abdomen were not particularly marked, some were hyperactive, which I cannot make much out of. Someone must have thought she had either common-duct colic or ureteral colic because calcium gluconate was given, intravenously, I presume. But as one might expect, it did her no good. She obviously was getting worse, and for that reason she was taken to the operating room for an exploratory laparotomy.

In summary, I think that she had something involving the intestinal tract. I do not believe it involved the stomach. It was not acute appendicitis with peritonitis, for I believe the condition had been going on too long. One always thinks of appendicitis, even in this elderly age group. It seems unlikely that it was a malignant lesion. At least we have insufficient evidence to make a diagnosis of

DR MALLORY That is possible. We found no evidence of infarct, however, which would help back up such an opinion.

DR MEANS Am I right in thinking that in the case we reported no such extensive process in the small arterioles prevailed? The process was largely confined to the right main pulmonary artery, which was totally occluded just as this one was. A point of interest in that case was that the bronchial artery was huge, about as large as my finger, and furnished nutrition to the lung adequately. In this patient the autopsy was done elsewhere, and the tissue was in such a state that you could not determine whether or not the bronchial artery was enlarged.

DR MALLORY In the microscopical sections we could identify apparently enlarged branches of the bronchial artery but were unable to identify the main trunk.

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CASE 35082

PRESENTATION OF CASE

A seventy-three-year-old widow entered the hospital complaining of epigastric pain with vomiting.

Four weeks prior to admission she suffered an episode of dull, nonradiating, epigastric pain with nausea, vomiting, diarrhea and a temperature of 101°F. She was seen by her physician, and a diagnosis of acute gastroenteritis was made. About one week later she began to experience almost daily episodes of steady, epigastric pain, lasting for two or three hours and relieved by morphine. These attacks were associated with nausea and occasional vomiting. There was probable aggravation of the pain by the taking of food. No history of right-upper-quadrant pain, fatty-food intolerance or jaundice was elicited. There were no previous symptoms suggestive of ulcer. She had lost about 15 pounds during the month prior to admission.

Twenty years previously a pelvic operation was performed, the exact nature of which was not known.

Physical examination revealed a senile, uncooperative, slightly disoriented, elderly woman. The heart was not enlarged, the aortic second sound was greater than the pulmonic second, and a Grade I systolic murmur was present at the apex. There was diffuse abdominal tenderness, most marked in the right lower quadrant and midepigastrium, with slight muscular spasm in the epigastrium. No masses were felt, and no peristalsis was heard. She was retching during part of the examination. A lower abdominal, midline scar was present.

The temperature was 98.6°F, the pulse 120, and the respirations 22. The blood pressure was 175 systolic, 80 diastolic.

Examination of the blood showed a hemoglobin of 14 gm and a white-cell count of 15,950, with 89 per cent neutrophils. Urinalysis was negative. A serum amylase was 45 units per 100 cc, the chloride was 104 milliequiv per liter, and the nonprotein nitrogen was 18 mg per 100 cc. A chest x-ray examination appeared normal. There was no free air under the diaphragm. A plain film of the abdomen showed a moderate amount of gas scattered throughout the large bowel. One small loop of gas-filled small bowel was present in the left upper quadrant. This did not have the appearance of a small-bowel obstruction. There was one small oval calcification, 3 mm in diameter, present in the right side of the abdomen adjacent to the right border of the second lumbar vertebra. This appeared to be outside the kidney. Its exact nature could not be determined.

Following admission she complained of increased abdominal pain. The white-cell count twelve hours after admission was 22,000, the blood pressure was 125 systolic, 70 diastolic, and the pulse 160. She was observed for several hours and was noted to have intermittent episodes of severe abdominal pain, which was apparently generalized and caused her to writhe in bed and to double herself up. During these episodes some hyperactive peristaltic sounds were heard. During this period the crampy pain was unrelieved by calcium gluconate intravenously. During the period of observation she developed obvious signs of shock characterized by a falling blood pressure and a rising pulse. About sixteen hours following admission an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR ROBERT R. LINTON This elderly woman obviously entered the hospital with some sort of acute abdominal condition, which, I believe, was surgical. The history is of interest in that the symptoms began one month before she was admitted to the hospital. They were characteristic of something affecting the gastrointestinal tract, since she had nausea and vomiting and associated with that she also had severe pain, apparently sufficient to require morphine — I presume by injection.

The past history is of interest in that there are symptoms suggestive of a lesion such as a duodenal or a gastric ulcer. Her dietary habits certainly make one think that she was not suffering from colitis or enteritis. I believe biliary-tract disease can be ruled out for the same reason. Perhaps of significance, especially to a surgeon, this patient with an acute abdominal condition (relatively acute at least) had had a pelvic operation twenty years before so that one cannot help considering in the differential diagnosis the possibility of intestinal

obstruction due to adhesions of the small intestine I think it is unlikely in this particular patient, but it is something one should always think of when one sees a scar on the abdomen with an acute abdominal condition.

The physical examination was essentially negative, I think, except for the fact that she had diffuse abdominal tenderness, most marked in the right lower quadrant and epigastrium. It is of significance that the temperature was normal—98.6°F. I presume that is to be relied upon and, if so, rules out the question of peritonitis at the time that she was admitted so that I doubt that she had a condition at that time that was producing peritonitis. The cardiovascular system was in a satisfactory condition for her age. The blood pressure was 175 systolic, 80 diastolic. She had not lost much blood, since the hemoglobin was 14 gm, unless she was dehydrated, which can elevate the hemoglobin. We have no other figure on the hemoglobin so if she was bleeding, I will have to leave that to Dr. Mallory to tell us about.

The serum amylase was 45 units per 100 cc. I believe in our laboratory the normal is somewhere in the vicinity of 30 units, is that right, Dr. Mallory?

DR. TRACY B. MALLORY: Yes.

DR. LINTON: The serum amylase was slightly elevated. Undoubtedly those taking care of her were thinking of acute pancreatitis, which one should consider in a patient complaining of epigastric pain and the other associated symptoms. I would say that 45 units of serum amylase was equivocal, it does not help one way or the other in making a diagnosis of pancreatitis. If she had pancreatitis beginning four weeks before admission, one would expect a normal serum amylase after that long a period. As a matter of fact, the determination usually returns to normal fairly promptly when an acute pancreatitis develops—I think within a matter of forty-eight hours. The other point regarding serum amylase is that it is a test that cannot be relied on too much to make a diagnosis of pancreatitis because there are other acute abdominal conditions, even biliary-tract disease, that give an elevation, as I believe this patient demonstrates, although the elevation was not very marked.

The nonprotein nitrogen was normal. From the surgical point of view the x-ray films are of interest in any patient who has an acute abdominal condition in which one suspects intestinal obstruction, and I think one would suspect it in this case.

DR. STANLEY M. WYMAN: The posteroanterior film of the chest shows the lung fields grossly clear. The heart shadow is not remarkable for a woman of this age. There is no evidence of gas beneath either leaf of the diaphragm. The liver shadow and the spleen do not appear unusual. The lateral view of the chest shows an increase in the anteroposterior diameter, I believe, in keeping with the patient's given age. Plain films of the abdomen

show again that the liver is grossly normal, and the spleen not enlarged. This one loop of gas-filled bowel certainly suggests small bowel, probably jejunum, and it is wider than usual, but I think it is insufficient evidence to make a flat-footed diagnosis of intestinal obstruction. I believe the small, round shadow of calcification described may possibly lie in cartilage. The bones are osteoporotic but show no definite destruction. I cannot identify any unusual soft-tissue masses.

DR. LINTON: A plain abdominal film in a patient whom one suspects of having intestinal obstruction is an extremely important diagnostic aid because by means of it one can frequently detect early intestinal obstruction and certainly can readily detect an advanced intestinal obstruction. My opinion on looking at these x-ray films and listening to Dr. Wyman's description of them is that this patient obviously did not have intestinal obstruction of sufficient degree to explain the nausea and vomiting—as well as the fact that she had diarrhea, which would be hard to connect with intestinal obstruction. The x-ray film on the left shows even less gas than one usually sees in a plain abdominal film. Do you agree?

DR. WYMAN: That is true. On the far right there is a little gas in the colon and in the one loop that represents presumable jejunum.

DR. LINTON: I feel quite sure then that we can rule out intestinal obstruction as the cause of her symptoms. The white-cell count twelve hours after admission was 22,000, indicating some pathologic process sufficient to increase the count which, as a matter of fact, increased from 16,000 to 22,000. Of extreme significance, I think, is the fact that the blood pressure dropped to 125 systolic, 70 diastolic, and that the pulse rose to 160. Something was going on within the abdomen that had produced these changes, which apparently had been rather dramatic as they came on within twelve hours of admission. Associated with that she had the terrific bouts of pain that made her writhe about. Her condition did not improve. The peristaltic sounds in the abdomen were not particularly marked, some were hyperactive, which I cannot make much out of. Someone must have thought she had either common-duct colic or ureteral colic because calcium gluconate was given, intravenously, I presume. But as one might expect, it did her no good. She obviously was getting worse, and for that reason she was taken to the operating room for an exploratory laparotomy.

In summary, I think that she had something involving the intestinal tract. I do not believe it involved the stomach. It was not acute appendicitis with peritonitis, for I believe the condition had been going on too long. One always thinks of appendicitis, even in this elderly age group. It seems unlikely that it was a malignant lesion. At least we have insufficient evidence to make a diagnosis of

cancer of the large or small bowel. I think the most likely diagnosis in this case is thrombosis of the mesenteric vessels, either veins or arteries. And in view of the fact that this condition had been going on for several weeks, I would say that it was venous thrombosis of the mesenteric vessels, probably the superior mesenteric vein.

DR CHESTER M. JONES: Is the first film at all suggestive of free fluid in the abdominal cavity? There is a ground-glass appearance over the entire abdominal area.

DR WYMAN: One cannot judge, because the film was taken for the chest primarily. Therefore, there was insufficient penetration of the abdomen, and one would find this appearance even in normal persons.

DR JONES: If that were an ordinary abdominal film, it would be exciting.

DR WYMAN: Absolutely.

DR F. DENNETTE ADAMS: Can you, so to speak, rule out obstruction when there is no dilated bowel? In other words, if this condition is present, does it work just as well in reverse?

DR WYMAN: I think one may miss dilated loops readily on a film taken in the supine or prone position. We have been fooled in such cases because the bowel was filled with fluid, obscuring the gas shadows to a great extent. If these people are placed upright, the fluid levels are readily apparent.

DR LINTON: The gas in the right-hand film is in the colon. Therefore, she could not have had small-bowel obstruction, and she was too sick to have had large-bowel obstruction, I believe.

CLINICAL DIAGNOSIS

Perforated carcinoma of stomach

DR LINTON'S DIAGNOSIS

Acute mesenteric thrombosis, venous

ANATOMICAL DIAGNOSES

*Infarction of small intestine, cause undetermined
Arteriosclerosis, generalized, severe aortic, slight
coronary and mesenteric*

Nephrosclerosis, moderate

Polyp of cecum

PATHOLOGICAL DISCUSSION

DR MALLORY: I do not see either Dr Scannell or Dr Moorman in the audience. They operated on this patient and found on entering the abdomen diffuse discoloration of the small bowel, beginning about 16 cm. below the ligament of Treitz and extending almost down to the ileum. They could not feel pulsations in the vessels of the mesentery. Going back to the aorta they were able to feel pulsations of the trunk of the superior mesenteric artery for a distance of 1.5 or 2 cm., where there was a zone that felt a little thickened where the pul-

sations disappeared. They made a diagnosis of thrombosis of the superior mesenteric artery and believed that any surgical treatment was impossible in view of the fact that the entire small bowel appeared to be involved. The patient died about twelve hours later.

At the time of autopsy the resident pathologist, having had experience with a very similar case, refused to dissect the mesenteric vessels until both surgeons taking part in the operation were present. The three of them then examined the vessels with extreme care, and no thrombus was found anywhere in the distribution of the mesenteric artery. On the other hand, the entire small bowel was completely gangrenous by that time. The veins of the mesentery were likewise entirely free from thrombi so that there appears to have been a functional occlusion of the mesenteric artery with no anatomic basis and a strong suggestion that it was spastic in origin. The question of spasm in an intra-abdominal vessel is one that has been debated a great deal. Many people are skeptical of it. Dunphy,* at the Peter Bent Brigham Hospital, was interested in it a few years ago and concluded that in many cases functional obstruction of the mesenteric artery alone could produce episodes of acute intra-abdominal pain, often preceding a final thrombosis. He argued that this might be spastic occlusion of the artery analogous to anginal attacks in the coronary arteries.

DR JONES: Were the arteries sclerosed?

DR MALLORY: They were markedly sclerosed.

DR LINTON: I still cannot believe that at the age of seventy-three a vessel can go into spasm, especially spasm sufficient to shut off a vessel.

DR MALLORY: The last time we reported such a situation the surgeons refused to believe it. That is why the resident insisted on their presence. They actually dissected the vessel under our eyes. We convinced them at any rate. Whether I can convince this audience, I do not know.

DR LINTON: It is a most extraordinary and interesting lesion. I have never heard of it.

DR JONES: Dr Linton commented that at this age there could not be spasm of the vessels. In coronary disease older people with stiff arteries get angina, not necessarily because of spasm but because of the extra demands on the artery at certain times, producing coronary insufficiency. After meals there may be a great demand on the mesenteric circulation that might be analogous.

DR LINTON: You mentioned that the superior mesenteric artery was occluded at the time of operation. It would be hard to imagine a vessel as large as my little finger being shut off by spasm, but I must admit one cannot refute the findings. Dr Mallory has reported. I still say that this is a most unusual and interesting case of vascular disease.

*Dunphy, J. E. Abdominal pain of vascular origin. *Am. J. M. Sc.* 192 109-113 1936.

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ENDS AND MEANS

THE correspondence printed elsewhere in this issue of the *Journal* mainly concerns the action of the American Medical Association in assessing each member twenty-five dollars, only secondarily or by implication do the writers of the letters refer to compulsory health insurance or any other phase of Government participation in medicine. By an ironic turn of circumstances, these men, who have no quarrel with the Association's stand on state medicine, strongly object to the so-called "enforced" contribution, part of which was earmarked by their spokesmen as an aid in the struggle against changes imposed by force from outside the profession. It is sobering to realize that the condemna-

tion expressed represents division among those who are otherwise united in their opposition to dictation.

Among the liberties that doctors at present possess is freedom to criticize — whether the object is the Government or their own spokesmen. The opinion is properly expressed through an official organ of a society of physicians, not in the correspondence columns of the lay press, the public, which in the final analysis will decide the grave question now facing the medical profession, should not be given an unwarranted impression of undue friction and bickering within the ranks.

The strength that is inherent in union should not be lost sight of in differences of opinion about the best means of serving the interests of the American public. Regarding the acceptability of the assessment, returns so far received in Massachusetts indicate an overwhelming vote of confidence, particularly on the part of the active practitioners. Additional effective ways of countering the arguments in favor of state medicine must be found. Perhaps the best method is individual action to achieve a common end, each physician being "chairman of his Public Relations Committee."¹ The physicians may justifiably point out to their patients the full implications involved, Americans, for whom such words as "social" and "socialized" have become so disarmingly familiar as to have few terrors, might well be impressed by the connotations of the word "compulsory" — the dangerous term that, as the correspondence referred to indicates, can cause discord even among those who are united on fundamental issues. If doctors, acting independently but inspired by unity of conviction and determination, could demonstrate to their patients the achievements of free medicine in America (and the consequent benefits to the people at large) and the best means of maintaining and extending these benefits, public pressure could cause legislators to consult the medical profession in the drafting of plans and regulations vitally affecting medical practice.

Thus might the American doctor and his patient be spared the evils of Government-directed medicine as reported by one who has witnessed them at first hand. "Had they [the British medical profession] analyzed the defects in their system, presented a well conceived plan for improvements, and then

stood fast against ill advised changes, the British people might now be receiving better care and the physicians might be happier about their working milieu "2

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- 2 Sweet W H Recent impressions of medical practice in Great Britain *New Eng J Med* 240 168-173, 1949

ANOTHER BULWARK AGAINST SOCIALIZED MEDICINE

SOUND public-health programs providing state-wide coverage can best be administered through the establishment of efficient and economic local health departments, employing full-time, trained and experienced personnel. The American Medical Association has for many years recognized the urgent need for this type of health coverage and strongly supports sound action to extend and strengthen local health services. This support has been expressed in numerous resolutions passed by the House of Delegates and is Point 2 of the Association's Ten Point Health Program.

Through the remarkable combination of complacency, inadequate legislation and local autonomy, Massachusetts has succeeded in ignoring its local health programs, which for the most part compare unfavorably with those established in other states. An article in a recent issue of the *Journal** outlined the severe deficiencies in this field that exist throughout the Commonwealth. Where does the fault lie?

Appreciation of the need for the promotion and support of adequate local health services in Massachusetts is with few exceptions limited to practicing physicians who have knowledge and interest in their local community's health programs. Unfortunately, their numbers are few.

The solution of this critical problem lies in community interests and action. It devolves upon the physician as a member of his community to exert efforts to help obtain adequate local health services. It befits him as a member of a society actively opposed to a threatened program of socialized medicine to support accepted and necessary measures that will ensure the free practice of medicine.

*Archibald, R. Fiore, A. and Skvirsky, S. L. Local health services in Massachusetts. *New Eng J Med* 239:858-861, 1948

The people purchase health service. Whether that purchase is accomplished directly between patient and physician or indirectly, through the tax dollar, it remains that health, as a commodity, constitutes big business, and the consumer's voice has grown louder in its demand for more service.

The physician has his choice. He may retain his complacency, ignore the demand and express open resentment of the threatened program of socialized medicine, or he may make constructive efforts to satisfy these demands by the promotion, at the local level, of adequate, basic health services through measures endorsed by the American Medical Association.

Such a program of full-time local health departments providing efficiently and economically administered health services is the physician's disturbingly obvious but as yet unrecognized weapon against the threatened advances on his right to practice independent of governmental control.

The following statement is quoted in full, as it appeared in the recent January 19 issue of the *Bulletin of the Middlesex East District Medical Society*.

Excerpts from Mr. Ewing's speech before the State and Territorial health officers in Washington: "Success of the government health plan depends on the people themselves and what they are willing to do about it." He then stated in brief that each community must be organized, and state and local campaigns of education must be planned, and that he is putting this up to the health officers to undertake this job in their states. There it is gentlemen, and what are we, as a Medical Society, going to do about it?

It should be pointed out that *any* health program "depends on the people themselves and what they are willing to do about it" and that physicians constitute a not unimportant segment of these people. Let them look to the stark inadequacies that exist in their own local health services for their answer to the question "What are we as a Medical Society going to do about it?"

While the Federal Security Administrator has thrown the challenge to state health officers to put across his program, there is no evidence that the health officers have accepted the challenge. As a matter of fact, health officers are the practitioner's strongest ally in his struggle against political inter-

ference. The failure on the part of many physicians to comprehend the basic underlying principles of public-health services has contributed enormously to the growth of the ever-lengthening shadow of governmental control of medicine.

Unwarranted criticism based on superficial knowledge assumes an importance second only to that of complacency in its power to destroy any unified group attack against the threat of political control.

Promotion of basic health services at the local level is sorely needed. With few exceptions, Massachusetts lags far behind other states in their efforts to satisfy these needs.

There are now before the Massachusetts General Court two bills that, if passed, will facilitate the promotion and maintenance of local health units throughout the Commonwealth. At the federal level, the eighty-first Congress has under consideration proposed legislation to further this program. Senator Virgil Chapman, who together with Senator Leverett Saltonstall and others has introduced the Local Public Health Units Act of 1949 (S 522), has commented that the "creation of such a system would constitute the surest bulwark against socialized medicine which many of us think is undesirable in America."

The physicians of Massachusetts have it within their power to strengthen that bulwark, through their support and interest in the program to provide all the people of the Commonwealth with basic local health facilities.

NATION-WIDE AND WORLD-WIDE PROGRAM FOR CONTROL OF INFLUENZA

ONE of the most important limitations of the protective value of vaccination against influenza is the occurrence of variations among strains of influenza virus. This fact became particularly prominent during the epidemic that occurred in the winter and spring of 1947. That epidemic was caused by a strain of influenza A that was antigenically distinct from the influenza A strains that had been incorporated in the polyvalent influenza vaccines in use prior to that time. The evidence came from

the demonstration that experimental animals immunized with the standard strains that were contained in commercial vaccines failed to protect against infection with the strain that was the cause of the 1947 influenza epidemic. What is more, the incidence of influenza among persons who had been vaccinated with the commercial vaccines shortly before this epidemic was the same as that among persons who had not been vaccinated. By contrast, during the epidemic of 1945-1946, which was due to influenza B, the protection conferred by the Lee strain that was incorporated in the standard vaccines seems to have been of high grade, as evidenced by the low incidence of influenza among vaccinated persons as compared with the unvaccinated controls during that epidemic.

Another limitation in the use of influenza vaccines is the relatively short duration of the protection that results from vaccination with influenza viruses. This necessitates the administration of the vaccines within a few weeks of an anticipated influenza epidemic, and since the exact time of occurrence of such epidemics cannot be predicted with certainty, it becomes necessary to repeat vaccinations in the fall of each year before the season for respiratory infections begins. One of the outstanding features of an influenza epidemic, when it occurs in any given area, is its explosive character. Adequate protection following vaccination, however, does not usually occur in less than one or two weeks. One cannot, therefore, expect to isolate an epidemic strain from any given area, prepare a vaccine from that strain that will pass potency and sterility tests and have the vaccine distributed and administered to the exposed population in the same area in time to do any good.

Fortunately, some pandemics in the past have been preceded by small and relatively localized outbreaks before the major epidemics reached their peak in the great centers of population. If these small outbreaks can be recognized early, the strains isolated and identified and their antigenic relation to known strains that are in use in the available vaccines determined promptly, it may be possible to choose from those available or to prepare more satisfactory vaccines for use in the major epidemic. This, in turn, may considerably increase the chance

for the vaccine to have a protective effect when the epidemic strikes

In this country the surgeons general of the Army, Navy, Air Forces and Public Health Service have developed a plan based upon this principle by which it is hoped to prevent a recurrence of a serious epidemic like that of 1918. This plan is part of an international program that was set up by the World Health Organization last year to study influenza and to aid physicians and health officers in the control of the disease. An influenza information center to serve as headquarters in the United States has been established at the National Institutes of Health in Bethesda, Maryland. The specific objectives of the world-wide program are to identify new strains of influenza virus as they appear, and to evaluate their usefulness for incorporation into influenza vaccines.

It is anticipated that as soon as a significant outbreak of a respiratory disease suspected of being influenza is reported in a given community, the Influenza Information Center will alert diagnostic laboratories in the region asking them to carry out serologic tests on patients for the presence of antibody against the influenza virus. Certain laboratories will also be asked to assign to the affected community a team of investigators experienced in the technics of isolating the virus. As soon as these investigators have isolated a new strain of virus they will send it at once for complete antigenic analysis to an established strain-study center of the Influenza Information Center, and appropriate strains of virus that have been isolated will be considered for possible inclusion in commercial vaccines.

The international influenza program was proposed during the Fourth International Congress for Microbiology in Copenhagen in July, 1947. Two months after that meeting, an international influenza center was established at the National Institute for Medical Research in London. The World Health Organization at its first World Health Assembly approved continuance of that center and recommended that all nations be invited to set up organizations to collaborate with it. In this country the appropriate authorities decided to establish the Influenza Information Center at Bethesda, Maryland, which would administer the program in this country and would serve as a liaison office

between the International Influenza Center and participating American laboratories.

Obviously the key to the success of this program is the co-operation of physicians in the early recognition and reporting of cases suspected of being influenza.

RED CROSS CAMPAIGN

THE annual campaign of the American Red Cross which will be conducted in March, once again draws attention to the needs, as well as the achievements of that organization. Community co-operation is essential in all work done by the Red Cross, whether it is educational or preventive (instruction in first aid, water safety, accident prevention, home nursing and nutrition) or remedial (aid to veterans, servicemen and civilians, both hospitalized and ambulatory). An illustration of the value of public partnership is provided by the fact that 64,000 persons have offered to donate blood, and that blood has been distributed to more than 350 hospitals. The Red Cross asks that the generous response in previous years be continued — that the people contribute the money, time and moral support necessary to make the 1949 campaign a success and to guarantee continued services in the future.

No one needs to be reminded of the achievements of the Red Cross where the need is greatest, the help is forthcoming. Last year more than three hundred disasters occurred in widely separated communities, and organized and efficient efforts were available in the work of the community volunteers and full-time staff of the Red Cross. Everyone is urged to contribute generously to this year's campaign; community need is met by community partnership, and when disaster strikes again, the help of the Red Cross will be vital.

MASSACHUSETTS MEDICAL SOCIETY

HOTEL ACCOMMODATIONS FOR THE ANNUAL MEETING

Headquarters for the one hundred and sixty-eighth annual meeting of the Society, to be held on May 24, 25 and 26, will be at the Hotel Sheraton, 50 Franklin Street, Worcester, Massachusetts. As accommodations in the hotel are limited, it is suggested that fellows wishing to attend the meeting reserve their rooms as soon as possible.

COMMITTEE ON ARRANGEMENTS

DEATHS

CARD — Walton G Card, M D, of Haverhill, died on November 11. He was in his sixtieth year.
Dr Card received his degree from Tufts College Medical School in 1925. He was a member of the staff of Hale Hospital and a fellow of the American Medical Association.
His mother, two brothers and one sister survive.

GILLON — Charles J C Gillon, M D, of Taunton, died on January 15. He was in his sixtieth year.
Dr Gillon received his degree from Harvard Medical School in 1915. He was chief of the Eye, Ear, Nose and Throat Service of Morton Hospital and consultant at Taunton State Hospital.
His widow, a son and a daughter survive.

MACKEY — William M MacKay, M D, of Waltham, died on January 31. He was in his sixtieth year.
Dr MacKay received his degree from Queen's University Faculty of Medicine, Kingston, Ontario, in 1914. He was senior physician of Middlesex County Sanatorium and a fellow of the American Medical Association.
His widow, three brothers and two sisters survive.

WELLER — John H Weller, M D, of Bridgewater, died on November 19. He was in his seventieth year.
Dr Weller received his degree from College of Physicians and Surgeons of Baltimore in 1909. He was senior physician at the Bridgewater State Farm and was a member of the New England Society of Psychiatry and a fellow of the American Medical Association.
His widow and a daughter survive.

POSTGRADUATE LECTURE COURSE

The fourth Postgraduate Lecture Course, which has been arranged by the Committee on Postgraduate Medical Education, Massachusetts Medical Society, in co-operation with the Massachusetts Department of Public Health, will begin on March 7. The meetings will be held at Sanders Theater in Memorial Hall, Harvard University, Cambridge. These lectures are designed for all physicians of Massachusetts and surrounding states, medical officers, hospital residents, interns, medical students and postgraduate students.

All those who plan to attend but have not enrolled should do so immediately by either returning the post card recently forwarded to all physicians in Massachusetts or addressing a post card or letter directly to Postgraduate Lecture Course Committee, Massachusetts Medical Society, 8 Fenway, Boston 15.

The detailed program for the course is as follows

- Monday, March 7 PUBLIC HEALTH** Chairmen James S Simmons and John F Conlin
- 7 00-7 30 Local Health Departments** Hugh R. Leavell, professor of public-health practice, Harvard School of Public Health
- 7 30-8 00 Maternal and Child Health** Samuel B Kirkwood, assistant professor of maternal health and instructor in obstetrics and gynecology, Harvard School of Public Health
- 8 00-8 30 School Health** Stuart S Stevenson, assistant professor of child health, Harvard School of Public Health.

8 30-9 00 Industrial Health Albert O Seeler, assistant professor of industrial medicine, Harvard School of Public Health.

Wednesday, March 9 CARDIOVASCULAR DISEASE Chairmen Laurence B Ellis and Eugene Eppinger

4 00-4 30 The National Heart Institute Paul D White, chief consultant, National Heart Institute, executive director, National Advisory Heart Council, and formerly clinical professor of medicine, Harvard Medical School, and physician, Massachusetts General Hospital

4 30-5 15 Preventive Measures in the Management of Heart Disease David Rutstein, professor of preventive medicine, Harvard Medical School.

5 15-5 30 The Role of the New England Heart Association in Sponsoring Local Heart Programs Laurence B Ellis, president, New England Heart Association, assistant clinical professor of medicine, Harvard Medical School, associate physician, Thorndike Memorial Laboratory, and assistant visiting physician, Boston City Hospital

5 30-6 00 The Diagnosis and Treatment of Angina Pectoris Joseph E F Riseman, associate in medicine, Harvard Medical School, and visiting physician, Beth Israel Hospital.

Monday, March 14 CARDIOVASCULAR DISEASE. Chairmen Laurence B Ellis and Eugene Eppinger

7 00-7 45 Curable Heart Disease C Sidney Burwell, research professor of clinical medicine, Harvard Medical School, and physician, Peter Bent Brigham Hospital.

7 45-8 15 The Use and Abuse of Laboratory Aids (Including Electrocardiography) in the Evaluation of Patients with Heart Disease Richard A. Bloomfield, instructor, Harvard Medical School, assistant physician, Thorndike Memorial Laboratory, and junior visiting physician, Boston City Hospital

8 15-9 00 The Diagnosis and Treatment of Rheumatic Fever — Its Complications Benedict F Massell, clinical associate in pediatrics, Harvard Medical School, associate research director, House of the Good Samaritan, and chief, Rheumatic Fever Division, Children's Hospital

Wednesday, March 16 INDUSTRIAL HEALTH AND ACCIDENTS Chairmen Henry C Marble and Daniel L Lynch

4 00-4 20 Industrial Health — Its Contributions and Opportunities Carl M Peterson, secretary, Council on Industrial Health, American Medical Association

4 20-4 40 Injuries to the Hand Edward Hamlin, assistant surgeon, Massachusetts General Hospital

4 40-5 00 Industrial Diseases Albert O Seeler, professor of industrial diseases, Harvard School of Public Health

5 00-5 20 Examination of Back Injuries Carroll Larson, assistant surgeon, Department of Orthopedics, Massachusetts General Hospital

5 20-5 40 Common Causes of Contact Dermatitis George E Morris, consultant in Industrial Dermatology, Boston

5 40-6 00 Records and Reports in Industrial Accidents Henry C Marble, consulting surgeon, Massachusetts General and Faulkner hospitals

Monday, March 21 INFECTIOUS DISEASES Chairmen Chester S Keefer and Louis Weinstein

7 00-7 25 Newer Antibiotic Agents — Polymyxin, Aureomycin and Chloromycetin Maxwell Finland, physician-in-chief, Fourth Medical Service, Boston City Hospital, and assistant professor of medicine, Harvard Medical School.

for the vaccine to have a protective effect when the epidemic strikes

In this country the surgeons general of the Army, Navy, Air Forces and Public Health Service have developed a plan based upon this principle by which it is hoped to prevent a recurrence of a serious epidemic like that of 1918. This plan is part of an international program that was set up by the World Health Organization last year to study influenza and to aid physicians and health officers in the control of the disease. An influenza information center to serve as headquarters in the United States has been established at the National Institutes of Health in Bethesda, Maryland. The specific objectives of the world-wide program are to identify new strains of influenza virus as they appear, and to evaluate their usefulness for incorporation into influenza vaccines.

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Obviously the key to the success of this program is the co-operation of physicians in the early recognition and reporting of cases suspected of being influenza.

RED CROSS CAMPAIGN

THE annual campaign of the American Red Cross, which will be conducted in March, once again draws attention to the needs, as well as the achievements, of that organization. Community co-operation is essential in all work done by the Red Cross, whether it is educational or preventive (instruction in first aid, water safety, accident prevention, home nursing and nutrition) or remedial (aid to veterans, servicemen and civilians, both hospitalized and able bodied). An illustration of the value of public partnership is provided by the fact that 64,000 persons have offered to donate blood, and that blood has been distributed to more than 350 hospitals. The Red Cross asks that the generous response in previous years be continued—that the people contribute the money, time and moral support necessary to make the 1949 campaign a success and to guarantee continued services in the future.

No one needs to be reminded of the achievements of the Red Cross where the need is greatest, the help is forthcoming. Last year more than three hundred disasters occurred in widely separated communities, and organized and efficient efforts were available in the work of the community volunteers and full-time staff of the Red Cross. Everyone is urged to contribute generously to this year's campaign; community need is met by community partnership, and when disaster strikes again, the help of the Red Cross will be vital.

MASSACHUSETTS MEDICAL SOCIETY HOTEL ACCOMMODATIONS FOR THE ANNUAL MEETING

Headquarters for the one hundred and sixty-eighth annual meeting of the Society, to be held on May 24, 25 and 26, will be at the Hotel Sheraton, 50 Franklin Street, Worcester, Massachusetts. As accommodations in the hotel are limited, it is suggested that fellows wishing to attend the meeting reserve their rooms as soon as possible.

COMMITTEE ON ARRANGEMENTS

4 25-4 45 Neoplasm of the Spine and Cord James L. Poppen, neurosurgeon, Lahey Clinic and New England Deaconess and New England Baptist hospitals

4 50-5 10 Injuries of the Spine and Cord Donald Munro, associate professor of neurosurgery, Harvard Medical School and Boston University School of Medicine, and chief, Department of Neurosurgery, Boston City Hospital

5 15-5 35 Infectious Lesions of the Spine and Cord James C. White, associate professor of surgery, Harvard Medical School, and chief, Neurosurgical Service, Massachusetts General Hospital

5 40-6 00 Ruptured Intervertebral Disk W. Jason Mixer, member, Board of Consultation, Massachusetts General Hospital, and consultant on staffs of Beth Israel, Mt. Auburn and New England Deaconess hospitals

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4 00-5 00 Allergy in Childhood Lewis Webb Hill, visiting physician and chief of Allergy Clinic, Children's Hospital, and clinical associate in pediatrics, Harvard Medical School

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8 00-8 25 Cardiology Samuel A. Levine, assistant professor of medicine, Harvard Medical School, and physician, Peter Bent Brigham Hospital

8 30-8 55 Endocrinology Elmer C. Bartels, physician, Department of Internal Medicine, Lahey Clinic and physician, New England Baptist and New England Deaconess hospitals. Frank N. Allan, executive director, Department of Internal Medicine, Lahey Clinic, and physician, New England Baptist and New England Deaconess hospitals, and Lewis M. Hurxthal, head of Department of Internal Medicine, Lahey Clinic, and physician, New England Baptist and New England Deaconess hospitals

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4 50-5 00 Question Period

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5 25-5 50 The Needs and Benefit of Medical Rehabilitation Augustus Thorndike, chief surgeon, Department of Hygiene, Harvard University

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YOUR LEGISLATORS

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Name

Address

Number of copies

7 30-7 55 Antibiotic Treatment of Pneumonia William Hewitt, instructor in medicine, Boston University School of Medicine, fellow, National Institute of Health, and staff member, Evans Memorial, Massachusetts Memorial Hospitals

8 00-8 25 The Treatment of Nephrosis by Induced Measles Charles A Janeway, Thomas Morgan Rotch Professor of Pediatrics, Harvard Medical School, and physician-in-chief, Children's Hospital

8 30-8 55 Use of Chemotherapeutic Agents as Prophylaxis Benedict F Massell, clinical associate in pediatrics, Harvard Medical School, associate research director, House of the Good Samaritan, and chief of the rheumatic fever division, Children's Hospital

Wednesday, March 23 MEDICOLEGAL PROBLEMS Chairmen Alan R Moritz and Richard Ford

4 00-5 00 The Doctor as Defendant and as Witness Richard Ford, associate medical examiner of Suffolk County, and member of teaching staff, Department of Legal Medicine, Harvard Medical School

5 00-6 00 Scientific Evidence in Criminal Investigation Russell Fisher, Rockefeller Fellow, Department of Legal Medicine, Harvard Medical School

Monday, March 28 HEADACHE Chairmen James L Poppen and John B Dynes

7 00-7 45 Headache Caused by Intracranial Neoplasms James L Poppen, neurosurgeon, Lahey Clinic and New England Deaconess and New England Baptist hospitals

7 45-8 25 Migraine and Histamine Headache John B Dynes, neuropsychiatrist, Lahey Clinic, and neurologist, New England Deaconess and New England Baptist hospitals

8 25-9 00 Headaches from a Psychiatric Standpoint Robert E Arnot, research fellow in psychiatry, Harvard Medical School and Boston Psychopathic Hospital

Wednesday, March 30 GYNECOLOGY Chairman Fred Simmons

4 00-4 20 Elementary Facts Concerning the Vaginal Smear Howard M Ulfelder, assistant surgeon, Massachusetts General Hospital, and clinical associate in surgery, Harvard Medical School

4 30-4 50 Conservative Ovarian Surgery Samuel R Meaker, professor of gynecology, Boston University Medical School

5 00-5 20 Conservative Management of Endometriosis John Fallon, director, Fallon Clinic, Worcester, Massachusetts

5 30-6 00 The Physiology of Menstruation (Animated Cartoon) John Rock, clinical professor of gynecology, Harvard Medical School, and Somers H Sturgis, assistant surgeon, Massachusetts General Hospital

Monday, April 4 OBSTETRICS Chairmen M Fletcher Eades and H Bristol Nelson

7 00-7 15 X-Ray Pelvimetry and Its Clinical Interpretation Robert H Barker, Boston Lying-in Hospital

7 15-7 30 Significance of Test of Labor Luke Gillespie, assistant in obstetrics and gynecology, Harvard Medical School, and assistant obstetrician, Boston Lying-in Hospital

7 30-7 45 Antibiotics in the Treatment of Uterine Sepsis Maxwell Finland, physician-in-chief, Fourth Medical Service, Boston City Hospital, and assistant professor of medicine, Harvard Medical School

7 45-8 00 Question Period

8 00-8 20 Nonmenstrual Bleeding Diagnosis and treatment John Rock, clinical professor of gynecology, Harvard Medical School

8 20-8 40 Treatment of Toxemia of Pregnancy Duncan Reid, Richardson Professor of Obstetrics, Harvard Medical School

8 40-9 00 Question Period

Wednesday, April 6 Gastroenterology Chairmen Francis D Moore and Chester M Jones

4 00-4 20 The Treatment of Bleeding Gastric and Duodenal Ulcer John E Dunphy, senior associate in surgery, Peter Bent Brigham Hospital, and assistant professor of surgery, Harvard Medical School

4 20-4 30 Discussion

4 30-4 50 The Value of Exfoliative Cytology in the Diagnosis of Gastric Carcinoma Howard M Ulfelder, assistant surgeon, Massachusetts General Hospital, and clinical associate in surgery, Harvard Medical School

4 50-5 00 Discussion

5 00-5 20 Nutritional Problems Arising from Anastomotic Surgery Chester M Jones, physician, Massachusetts General Hospital, and clinical professor of medicine, Harvard Medical School

5 20-5 30 Discussion

5 30-5 50 Body-Fluid Replacement in Gastrointestinal Surgery Francis D Moore, surgeon-in-chief, Peter Bent Brigham Hospital, and Moseley Professor of Surgery, Harvard Medical School

5 50-6 00 Discussion

Monday, April 11 HEMATOLOGY Chairmen Joseph F Ross and Clement A. Finch

7 00-7 20 The Therapeutic Use of Folic Acid and Vitamin B₁₂ William B Castle, professor of medicine, Harvard Medical School, and director, Thorndike Memorial Laboratory and Second and Fourth Medical Services (Harvard), Boston City Hospital

7 20-7 40 Hemolytic Disorders Practical applications of the Coombs test and other serologic techniques. Charles P Emerson, Jr, assistant professor of medicine, Boston University School of Medicine, and visiting physician, Massachusetts Memorial Hospitals

7 40-8 00 The Clinical Use of Blood Fractions Charles A Janeway, Thomas Morgan Rotch Professor of Pediatrics, Harvard Medical School, and physician in chief, Children's Hospital

8 00-8 20 Dicumarol and Heparin — Their Use and Abuse Clement A Finch, associate in medicine, Harvard Medical School, and associate in medicine, Peter Bent Brigham Hospital

8 20-8 40 What Can be Accomplished in Treating Leukemia and Malignant Lymphoma Joseph F Ross, associate professor of medicine, Boston University School of Medicine, and physician, Massachusetts Memorial Hospitals

8 40-9 00 Practical Management of the Rh Problem Louis K Diamond, assistant professor of pediatrics, Harvard Medical School, physician and chief of Hematology Division and director of the Blood Bank, Children's Hospital

Wednesday, April 13 DISEASES OF THE SPINAL COLUM Chairmen W Jason Mixer and James C White

4 00-4 20 Congenital Anomalies of the Spine and Spinal Cord Franc D Ingraham, associate professor of surgery, Harvard Medical School, neurosurgeon-in-chief, Children's Hospital, and neurologic surgeon, Peter Bent Brigham Hospital

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CORRESPONDENCE

ASSURANCE NEEDED

To the Editor Enclosed is a copy of a letter sent to the Secretary of the American Medical Association and signed by fifteen Springfield physicians, which is forwarded for publication in your columns in case you consider it of sufficient interest

Howard N Simpson, M D
Springfield, Massachusetts

George F Lull, M D
Secretary and General Manager
American Medical Association
535 North Dearborn St
Chicago 10, Ill

Dear Dr Lull

The undersigned physicians, members of the American Medical Association, have received your letter and the enclosed literature regarding the \$25 00 assessment voted by the House of Delegates, which you choose to describe as "the democratically chosen body that speaks for the American Medical Association" The dictionary definition of "democratic" is "chosen by the people" which the House of Delegates is not and can not be according to the Association's by-laws We have no desire, at the present time, to make an issue of this, but merely wish to point out that these delegates, whom we did not elect, have seen fit to demand our support and our money, but have evinced no interest whatsoever in our opinions as to whether the assessment was justifiable or how it was to be spent Because we believe that quarreling and disunity among ourselves at this time would be disastrous we shall pay the assessment provided we may have assurances, either privately or through the press, that our money will be used in a more enlightened manner than your letter implies

Let us make it clear at this point that the undersigned are physicians deriving all, or nearly all, their income from private practice We believe in private practice, we believe in the high standards of American medicine, and we view with profound concern the impending threat to these standards inherent in any universal method of government financing and control of medicine

We also believe that the fundamental issues are becoming beclouded in the barrages and counter-barrages detonated by Mr Ewing on one side and Dr Fishbein on the other We believe no useful purpose is served by hurling insults and ridicule either at public officials or at private doctors

We believe that the American Medical Association, with its all-too-recent embrace of the Blue Cross and Blue Shield plans, is at a very definite disadvantage in the public mind

We believe that there is at the present time in this country a very definite political trend to the left Whether we like it or not we must face the facts and deal with them We hold it to be highly questionable whether a group such as the presently constituted House of Delegates is capable of successfully challenging such a political trend

We believe that the course of action outlined in your letter will lead only to defeat The public is tired of sneers, of clichés, and of propaganda A large segment of the public — the voting public — believes that the cost of medical care is too high They realize that the medical profession in America has made great advances in science, but has contributed almost nothing to the solution of the economic problems of the ill

We believe that organized medicine needs leadership and an enlightened attitude toward modern problems, that our duty to our patients and to ourselves is not to fight blindly against the administration and the trend of history, but rather to formulate a specific legislative program which is positive, forward-looking, practical, and humanitarian There are portions of the Ewing program, such as extension of public health services and improved distribution of trained manpower, which the vast majority of the profession would be willing to accept, there are changes in the present medical economic set-up which the public demands We believe that by substituting harmony

for hatred, and co-operation for conflict many of the problems may be resolved

Finally, we believe that we are better trained equipped to consult than to fight We believe that 81st Congress would be more favorably influenced by subtler suasions of the bedside manner than by the pourings of a California propaganda mill

Changes will be made, and in these changes it is better that we lead than that we be driven There is another way that American medicine can maintain its place in the world, or that we, as individuals can practice profession with dignity and with honor

Very sincerely yours,

HOWARD N SIMPSON, M D
RAYMOND L BARRETT, M D
WILLIAM J DEVLIN, M D
FRANK J JORDAN, JR, M D
EDWARD J FERRARONE, M D
BARRON D KNOX, M D
HORACE B PEASE, M D
CHARLES C DERRICK, M D
HARRY L ROBERTS, M D
W O WILDER, M D
JAMES L SMEAD, M D
ALLEN S JOHNSON, M D
WAYNE C BARNES, M D
FREDERICK D JONES, M D
THEODORE R MINER, M D

NOTE Delegates to the American Medical Association are elected by the council of the state society The council are the representatives of their district society — Ed

NOTICES

ANNOUNCEMENTS

Dr Frank P Cahill announces the opening of his office for the practice of general surgery at 395 Commonwealth Avenue, Boston

Dr Thomas E Caulfield announces the opening of an office at 520 Commonwealth Avenue, Boston, for the practice of psychiatry

Dr Francis R Kenney announces the opening of an office for the practice of general surgery at 319 Longwood Avenue, Boston

Dr C Purcell Roberts announces the removal of his office from 26 Linden Avenue, N E, to 762 Cypress Street, N E, Atlanta, Georgia

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, March 3, at 7 15 p m, in the classroom of the Nurses' Residence Dr Marianne Taylor will speak on the subject "Gynecologic Conditions Viewed from the Psychosomatic Angle" Dr Lucile Lord-Heinstein will be chairman

AMERICAN ACADEMY OF PEDIATRICS

Publication of the national report on the findings of the recently completed two-and-a-half-year study of child health services will be marked by a dinner on April 2 in New York City, according to an announcement of Dr Warren R Sisson, president of the American Academy of Pediatrics A nationally known layman and an outstanding authority in medicine and public health are being invited to be guest speakers The two-volume report, which is now in press, is being published by the Commonwealth Fund of New York

(Notices concluded on page xiii)

The New England Journal of Medicine

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Volume 240

MARCH 3, 1949

Number 9

THE TREATMENT OF HYPERTENSIVE CEREBROVASCULAR DISEASE BY SPLANCHNICECTOMY*

MAX M. PEET, M.D.,† AND EMIL M. ISBERG, M.D.‡

ANN ARBOR, MICHIGAN, AND MIAMI BEACH, FLORIDA

THE occurrence of a cerebrovascular accident is an ominous incident in the life history of a patient with arterial hypertension. It is the cause of death in almost a third of all hypertensive persons. As for those who survive such an accident, clinical experience has led to the belief that recurrences are likely and that mortality increases with each subsequent stroke.

Many hypertensive patients who had already sustained definite cerebral accidents have presented themselves at the University of Michigan Hospital, asking some preventive to ward off a recurrence. Many of these patients with hypertensive cerebrovascular disease have been treated with the surgical procedure of bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy, in the attempt to alter beneficially the course of the disease. These patients have now been followed for a number of years, and their course subsequent to operation is the basis for this report.

To determine whether a sympathectomy has modified the natural history of hypertensive cerebrovascular disease, the course of patients not operated on must first be known. The literature on the duration of life after cerebrovascular accidents is almost entirely based on autopsy records, such reports are concerned only with patients who die after apoplexy. Thus, these records are not entirely valid for determining prognosis and mortality. Also, the several reports in the literature on survival in hypertension in general do not distinguish the patients with cerebrovascular disease.¹⁻⁶

Because the literature does not provide a completely adequate control for purposes of comparison, Griep, Barry and Hall⁷ have collected a group of 117 hypertensive patients who were first studied

at the University of Michigan Hospital ten or more years ago, and who were not treated with a splanchnicectomy. Six patients in this series had sustained a cerebral accident prior to the first examination. Of 4 women, 2 were still living ten and eleven years since the initial examination, the other two survived one year and eight years respectively. Both male patients were dead, having lived for seven and eight years respectively after their first examination. A cerebral accident was the cause of death in each case.

Brown⁸ has reported on 120 patients admitted to the Henry Ford Hospital, Detroit, between 1934 and 1939, each case clinically diagnosed as cerebral hemorrhage, an elevated blood pressure above 150 systolic and 100 diastolic was present in 90 per cent of the cases. He found that 65 per cent of patients recovered from their first cerebral accident, and 52 per cent from their second one. Only 10 per cent survived a third stroke, and the mortality was 100 per cent for a fourth stroke. The intervening time between strokes ranged from a week to eighteen years, and the average interval was two and a half years. This report is mentioned to point out that once a hypertensive cerebral accident occurs, recurrences are frequent and mortality increases with recurrence. Therapeutic effort to ward off recurrence of hypertensive apoplexy is thus warranted.

MATERIAL

During the ten years intervening between November, 1933, and November, 1943, more than 1000 hypertensive patients were treated by splanchnicectomy at the University Hospital, and 135 had previously sustained a definite cerebrovascular accident in which neurologic signs persisted for at least seventy-two hours. Cerebral incidents of shorter duration and episodes of hypertensive encephalopathy are not included. A duration of seventy-two hours is used to differentiate cerebrovascular accidents from cerebrovascular episodes.

*From the Department of Surgery, Section of Neurosurgery, University of Michigan Hospital and Medical School.

This study was aided by grants from the United States Public Health Service and Mr. and Mrs. Albert Warner.

†Professor of neurosurgery, University of Michigan Medical School.
‡Research associate in hypertension, Section of Neurosurgery, University of Michigan Medical School; formerly instructor in internal medicine, University of Michigan Medical School.

Types of Cerebrovascular Accident

Sixty-six patients had sustained a hemiplegia, with coincident aphasia in 8. Hemiparesis had occurred in 50, a facial paralysis in 7, and aphasia alone in another 6 cases. There were 6 cases of spontaneous subarachnoid hemorrhage, the spinal-fluid findings in each confirming the diagnosis.

Age

The youngest patient was nineteen years, and the oldest was fifty-five years. Seventy-eight per cent

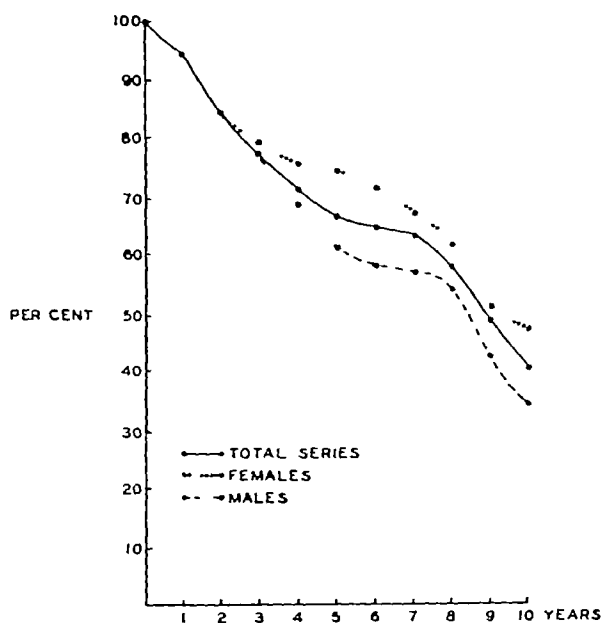


FIGURE 1 Curves of Yearly Survival Rates after Splanchnicectomy in 135 Cases of Hypertensive Cerebrovascular Disease

of this series were forty years and older at the time of the operation.

Sex

There were 73 male (54 per cent of the series) and 62 female patients.

Blood-Pressure Distribution

The average blood pressure ranged from 290 systolic, 178 diastolic, down to 170 systolic, 106 diastolic. Seventy-eight per cent had diastolic levels of 120 and higher.

Interval between Cerebrovascular Accident and Operation

Fifty-three per cent had a splanchnicectomy within six months of the cerebral accident, and 12.5 per cent were operated upon four to six weeks after the cerebral accident. The longest duration between apoplexy and operation was four years.

OPERATION AND OPERATIVE RISK

The operative procedure consists of bilateral resection of the greater, lesser and least splanchnic nerves, and excision of the lower thoracic sympathetic ganglions. During the first six years of operation was performed, only the lower thoracic dorsal ganglions were removed. Subsequently, ninth dorsal ganglions were also excised routinely. In recent years the operation has been extended to include a routine excision of the eighth dorsal ganglions. Higher ganglions, such as the seventh and fifth, are now frequently excised, depending on the technical facility in the individual case.

The anatomic dissection is carried out entirely above the diaphragm. This technic of splanchnic resection is performed bilaterally in one stage.

Three operative deaths occurred in this series of 135 hypertensive patients with cerebrovascular disease (operative mortality of 2.2 per cent). The patients were fifty-three, fifty-four and fifty-five years old, and in addition each had definite organic heart disease. The cause of death in each case was probably a cerebrovascular accident; autopsy, performed in 1 case, revealed thrombosis of the right middle cerebral artery and extensive recent infarction of the area supplied by the artery.

There were three additional postoperative cerebrovascular accidents, which the patients survived—cerebral thrombosis with left hemiparesis, a thrombosis of the anterior spinal artery and a left-facial muscle paralysis.

The operative mortality for hypertensive patients in general has been 1.6 per cent for those without papilledema, and 10 per cent for those with malignant hypertension.

SURVIVAL AFTER SPLANCHNICECTOMY

In this group of patients, each with a preoperative history of a definite cerebrovascular accident, the five-year survival rate for 62 female patients was 74.3 per cent, and the ten-year survival rate for 23 female patients was 48 per cent (Fig. 1). The five-year survival rate for 73 male patients was 61.8 per cent, and the ten-year survival rate for 23 male patients was 34.8 per cent.

For the entire series, the five-year survival rate was 67.3 per cent, the seven-year survival rate was 63.5 per cent, and the ten-year survival rate was 40.5 per cent. It should be noted that 16 cases with papilledema are included in this series.

Unfortunately the 6 cases of hypertensive cerebrovascular disease followed by Griep et al., in which operation was not performed constitute too small a group for purposes of comparison.

Forty-three patients, or approximately a third of the entire series, have suffered a recurrence of cerebrovascular accident during the long period subsequent to neurosurgical treatment, and 38 of these have died. Fifty per cent of the deaths in

Series have been caused by recurrence of a cerebrovascular accident, 37 per cent of the deaths been due to congestive heart failure and primary thrombosis

FACTORS INFLUENCING SURVIVAL

It is well known that hypertensive disease is much more serious in men than in women. The women in this series also had a better survival rate than men (Fig 1). It is interesting to note that a current cerebral accident was the cause of death in 70 per cent of the women who died. Yet only 10 per cent of the deaths among male patients were the result of another cerebrovascular accident, heart disease being the main cause of death.

Diastolic Blood Pressure

The mortality for the 135 patients with hypertensive cerebrovascular disease increased proportionately to the height of diastolic blood pressure at the time of operation. The five-year survival rate was 87.5 per cent for patients with diastolic levels below 120, 70.5 per cent for those with diastolic levels of 120 to 134, 66.5 per cent for those with diastolic levels of 135 to 149 and 46.5 per cent for the patients with diastolic levels of 150 and higher (Fig 2).

Retinal Hemorrhages

The presence of retinal hemorrhages at the time of splanchnicectomy adversely influenced the subsequent survival rate (Fig 3). The 64 patients with retinal hemorrhages had a five-year survival rate of 59.5 per cent, whereas the 71 patients without retinal hemorrhages had a five-year survival rate of 74.5 per cent. The ten-year survival rates were 29.3 per cent and 48 per cent, respectively. The preoperative fundoscopic examination through dilated pupils was performed in each case by staff members of the Department of Ophthalmology.

Heart Disease

Prolonged survival after a cerebral accident and subsequent sympathectomy is markedly dependent upon whether or not organic heart disease is coincidentally present (Fig 3). There were 107 cases in which definite heart disease existed at the time of the operation, this diagnosis in each was confirmed by an abnormal electrocardiogram or teleroentgenogram showing cardiac enlargement or both. The five-year survival rate for these persons was 58.8 per cent. On the other hand only 1 patient of the 28 with normal hearts died within five years of operation. The five-year survival rate for patients with previous cerebrovascular accidents but no coincident heart disease was 96.5 per cent.

Impaired Kidney Function

There were 51 patients with impaired kidney function, as evidenced both by an inability to concentrate urine to a maximum specific gravity of at least 1.020 on an eighteen-hour concentration test¹⁰ and by urea-clearance values of less than 60 per cent of average normal, these 51 persons had a five-year survival rate of 49.3 per cent. For 84 cases with normal kidney function, the five-year survival rate was 77.5 per cent. The 43 patients who had both heart disease and kidney disease coincident with the hypertensive cerebrovascular disease had a five-year survival rate of 41 per cent. There were 3 patients with azotemia at the time of the opera-

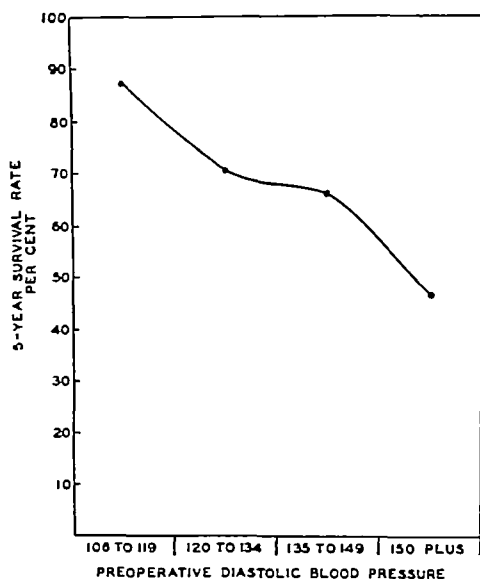


FIGURE 2 Influence of Preoperative Diastolic Blood Pressure on the Five-Year Survival Rate of 135 Patients with Hypertensive Cerebrovascular Disease

tion whose blood nonprotein nitrogen levels were above 40 mg per 100 cc, 1 case was an operative death, the second patient died within three months, and the third survived for three years.

Age

The mortality increased proportionally with the age at the time of splanchnicectomy (Fig 3). All 4 patients who were nineteen to twenty-nine years old survived for five years. The 25 who were in the fourth decade at the time of the operation had a five-year survival rate of 76 per cent, and those in the fifth decade a rate of 69 per cent. Fifty-four per cent of the 37 who were in their sixth decade survived for five years.

Interval Between Apoplexy and Splanchnicectomy

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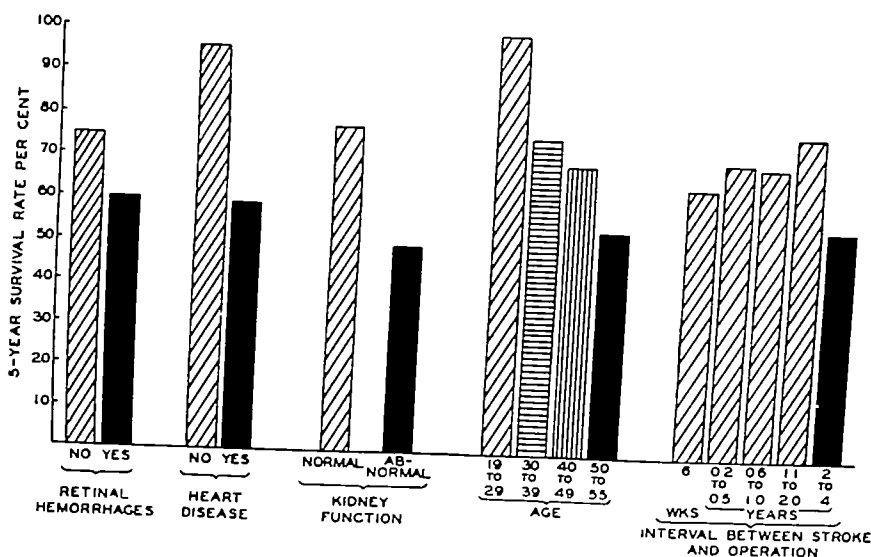


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The 65 patients still living five to thirteen years after splanchnicectomy performed subsequent to a cerebral accident have recently been examined. Fourteen, or 10.4 per cent of the entire series, are maintaining normal blood-pressure levels of less than 150 systolic, 90 diastolic. Two of the patients maintaining normal blood-pressure levels were operated upon in 1937, each six months after a cerebrovascular accident, and the preoperative blood-pressure levels averaged 225 systolic, 148 diastolic, and 185 systolic, 120 diastolic, respectively.

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thectomy must thus stem from an improvement in the general circulation following operation.

It has been demonstrated in this series that the persons who continue to live a long time after splanchnicectomy without recurrence of cerebral accidents also continue to maintain significant reduction of their blood pressure, with only a few exceptions. In a previous study of cardiac aspects in cases of arterial hypertension treated by splanchnic resection,¹¹ it was found that there was significant improvement in electrocardiograms and decrease in heart size after operation.

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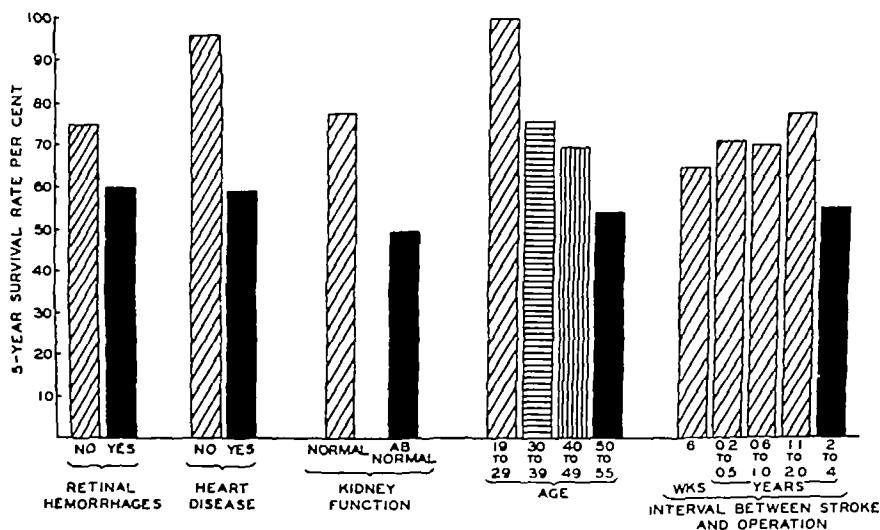


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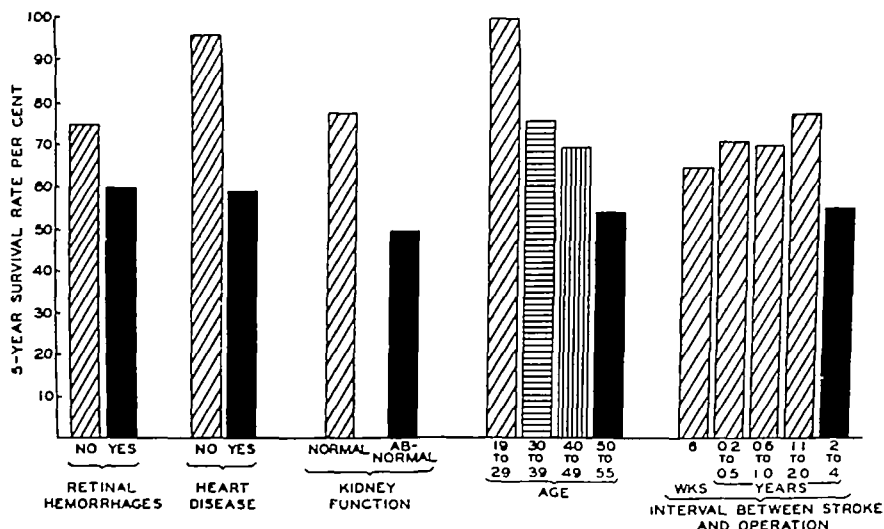


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PUBLIC FINANCING OF MEDICAL EDUCATION, RESEARCH, HEALTH AND MEDICAL CARE*

ALLAN M BUTLER, M D †

BOSTON

DISCUSSION of the bills pertaining to medical education, research, health and medical care that are now before the Congress indicates a considerable public interest in these matters. The increase in the effectiveness of modern medicine and in the cost of medical care has forced this interest upon the public. The public is not only interested as consumer but also as financier. The fact that in 1946 the public through Government contributed some \$1,200,000,000 for health and medical care is a measure of the failure of philanthropy and private charity to meet the needs.

The increase in the number of hospitals over the country at large faced with bankruptcy and in the number of medical schools having difficulty balancing their budgets has emphasized the need of financing medical care and education in a more systematic manner than in the past. When we are still in a period of inflation, when the country is seriously short of physicians and when medical education must be both expanded and improved if the medical needs of the people are to be satisfied, some of the wealthiest medical schools are being forced to curtail their budgets and most teaching hospitals in the country are faced with an annual deficit that threatens solvency. One of the large teaching hospitals in the past year had a deficit approximating one million dollars.

In the last few years, the opposition to Government as the logical agency in a democracy to collect funds from the public for medical education and research and from those whose health permits productive effort to finance those who suffer the misfortune of illness has lessened markedly. The public and the American Medical Association have within the past few years approved Government financing of hospital construction on a national basis, Government financing of medical education and medical research by grants from the Federal Security Agency and the proposed National Research Foundation, Government extending its support of maternal and child care through the Children's Bureau of the Federal Security Agency, and Government extension of public-health services. The American Medical Association has also, in endorsing the Taft National Health Act of 1947, approved Government financing of medical care for

low-income groups. Incidentally, the approval of these five things means that the American Medical Association has now endorsed five of the six parts of the original Wagner-Murray-Dingell Bill. In view of the bitter denunciation of this bill by the medical profession, endorsement of so much of the original bill is indeed noteworthy.

The question before us today, therefore, is not whether we will or will not have Government-financed medical care, it is rather how Government-financed medical care will be accomplished.

Must it continue in the more or less haphazard manner by which it has been accomplished up to date, or can it be done in a more orderly and coordinated manner?

Mr. Bernard Baruch, speaking in November to the County Medical Societies and Hospital Association of New York City, said

There is no question — the need for more medical care exists. Also, there is no question this need will have to be met. The problem is how.

In the matter of adequate medical care, too many doctors have been fighting a rear-guard action for too long. I feel I must warn those doctors — time is running against them. The medical profession has justly earned great influence in the community. It can keep that hold only as it moves forward. It will lose that hold if it has nothing but objections to offer, if it has eyes only for what not to do.

We must look for what can be done — and do it.

The great question is how? I do not want to seem to say I know the answers. We do know the public is demanding better and more medical service through some action — political or otherwise.

Even the least ambitious schemes for improving the nation's health require more doctors, all competently trained. Why aren't more doctors being educated? In studying that question, I was struck by how expensive training a doctor has become — in dollars and in time.

Professor Edwards A. Park, emeritus professor of pediatrics, at Johns Hopkins University School of Medicine, speaking at the New York Academy of Medicine in the spring of 1948, stated

The private medical schools must have state aid. At Johns Hopkins the tuition is \$600.00 a year. The cost to the medical school of the education of the student is \$3,900 per year. With the shrinking resources and the disappearance of the old private supports and without the addition of new, the full-time medical schools cannot continue.

The State must aid the student financially, because of the long, costly preliminary years of preparation, if medicine is to attract the finest of our young men. During four years in Johns Hopkins Medical School, the cost of the expenses of the medical student, apart from tuition, is from \$1,300 to \$1,500 a year. During his hospital training as intern, he receives no stipend. Only to those who command financial resources and can wait the years of preparation is a medical career open.

*Presented at a meeting of the Suffolk District Medical Society as part of a symposium on Current Congressional Medical Legislation. Harvard Club of Boston, May 1, 1948.

†Professor of pediatrics, Harvard Medical School, chief Children's Medical Service, Massachusetts General Hospital.

The New York Academy of Medicine's report on "Medicine in the Changing Order" states

There seems no alternative other than government aid if educational standards are to be raised or even maintained. If medical schools are to continue as centers of research here also government aid may be necessary.

A beginning is being made in such financing of medical education and research under existing legislation through the United States Public Health Service and the National Institute of Health. The bill pertaining to financing medical education that has recently been introduced in the Congress is the most recent development. Thus far in the manner in which admirably qualified committees have approved the applications for scholarships or grants to support teaching and research has given little ground for criticism. Will the Congress defend the professional direction of this federal support or will it permit its members or members of the administrative branch of the Government to channel the grants to specified fields of medicine that have a popular appeal? If so, Government-financed medical education and research may be as compartmentalized by sentimental appeal as is the research financed by the high-pressure drives for infantile paralysis, cancer and, recently, heart disease. The bill pertaining to heart disease certainly demands careful thought. If we start piecemeal, according to the dictates of pressure groups without due thought, the possibility of systematically financing medical research on a broad co-ordinated basis by Government support may be postponed for years.

As a pediatrician I am particularly interested in improving the training of physicians in the health and medical care of infants and children. The recommendations of the Executive Committee of the American Academy of Pediatrics concerning federal support of pediatric teaching were based on a survey recently completed, under the joint auspices of the American Academy of Pediatrics, the United States Public Health Service and the Children's Bureau, of the facilities for training physicians in the care of infants and children in the United States. Dr. John A. Toomey, president of the Academy, reports that this survey "has revealed a critical need of funds for the support of pediatric departments in the medical schools and the improvement of pediatric teaching of medical students." The Committee for the Improvement of Child Health and the Executive Board of the American Academy of Pediatrics have, therefore, submitted a recommendation for federal support of pediatric education. The report states

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BOSTON

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The private medical schools must have state aid. At Johns Hopkins the tuition is \$600.00 a year. The cost to the medical school of the education of the student is \$3,900 per year. With the shrinking resources and the disappearance of the old private supports and without the addition of new, the full-time medical schools cannot continue.

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The New York Academy of Medicine's report on "Medicine in the Changing Order" states

There seems no alternative other than government aid if educational standards are to be raised or even maintained. If medical schools are to continue as centers of research here also government aid may be necessary.

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Wagner, Murray, Truman and Baruch being unionists

Taft National Health Act states, as you know, "that it is the policy of the United States to have the States, through consultative services and grant-in-aid, to make available medical, hospital, dental and public-health services to every individual regardless of race or economic status" This will be accomplished under state-wide programs that will provide "(a) hospital services, surgical services and medical services for all those families and individuals in the State having insufficient income to bear the whole cost of such, and (b) periodic physical examinations for all children in elementary and secondary schools in the State" And it is further specified "Such program shall provide for collection of proper charges of less than the actual cost of such services from persons unable to pay in whole, but able to pay in part therefor" The federal contribution to the costs of these programs will come from general tax funds. Each State is left to collect its portion of the costs as it seems to fit. No mention is made in the bill of definition of eligibility other than mention that the services are to be provided for families and individuals with low incomes. So the question of whether this bill is intended for 20 per cent or 70 per cent of the cost of care is left open. Eligibility, however ultimately defined, will have to be reassessed continually according to the shifting earning capacity and expenses as affected by employment and illness. And each time the eligibility will have to be defined in terms of the Government's contributing 10, 25, 50, 75 or 100 per cent of the costs of the care at the moment. Thus, the bill provides "free medicine" to an indefinitely and difficultly defined portion of the public. Moreover, the federal Government is denied means of defending the quality of this free medicine. Finally there is no provision for improving medical care by supporting medical education and research except for some very inadequate support for dental research. The following is Dr. Park's opinion of the bill.

If the bill were passed as it stands, there could be as many different systems of medical care as there are states. Some of these in the more progressive states would probably be very good, in some other states exceedingly poor, and all would be laid open to the possibility of political intrigue and inefficiency. If the passage of the Wagner-Murray-Dingell Bill would produce chaos in medical care, the Taft Bill would produce national confusion and perhaps corruption, and would establish an inefficiency which it might be impossible to overcome. It would span the way to the perpetuation and extension of the poor features of the present system of medical care without the assurance of new good features. The bill is an example of careless thinking, or not thinking at all, and the fact that such a manifestly inferior measure could be proposed by our legislators is depressing to those who perceive how glorious a medical care program might be.

In an article in the *Yale Review*, ex-Governor Arnall states

There is a wide gulf between the proposals of some liberals for universal medical care and the proposals of some Radical Tories for subsidization of medical costs in the lower-income groups, a form of Bismarckian State Socialism repugnant to all American concepts, however well intended and however beneficial to the subsidized groups at the expense of the main body of citizens.

The Democratic party can, with propriety, support a measure, such as President Truman recommends, to include the cost of medical care in the general Social Security program of the country. The desirability of a specific measure would depend upon the cost of the program, the details of administration, etc. But, in theory, there is nothing objectionable about such a program. On the other hand, a program to subsidize medical care of those who are in depressed groups, to establish such a subsidy as a national policy and thereby give aid and comfort to those who believe that a handout is the appropriate substitute for justice, is not in accord with the basic beliefs of those who think that America can fulfill its promises of individual freedom and social responsibility.

Neither the National Health Insurance Act (S 1320) nor the Taft National Health Act (S 545) is compulsory regarding use of provisions by the public or participation by doctors. Both provide compulsion for collection of funds from the public. Indeed, the compulsion is similar to that pertaining to public education. Hence the designation of the former as a compulsory program and the latter as a voluntary one appears odd. Under both bills the federal Government's role is largely collection and allocation of funds. Under S 1320 there are a few provisions whereby the federal board with the advice and consent of the advisory council may designate standards in the interest of quality of care and efficiency of service. This kind of federal administration of grant-in-aid programs to states has been going on for years. The charge that either of these national health programs would establish a federal autocracy that would dominate American medicine and a federal bureaucracy that would bog it down seems to miss the serious administrative difficulties. The serious administrative problems under either bill will be at the state and local levels rather than the federal level.

In using these two bills as examples of the divergent manner in which Government financing of medical care may be approached and the emotional reactions that this problem may evoke, my personal point of view may be apparent. That however is not important. What is important is that we are at the crossroads where the decision must be made to proceed either along the way of a broad, clearly defined policy of more adequately financing medical education, research and care or along the way of ill defined temporary expediency. The former will require considered thought, tolerant discussion and much public debate. Diversity of opinion should be not only expected but also encouraged. For as President Conant of Harvard remarked in his annual report of this year, "In a democracy with our traditions only those reasoned convictions which emerge from diversity of opinion can lead to that unity — so essential for the welfare of the country." In this connection the medical

diagnosis with treatment The American Medical Association will endorse Senator Saltonstall's school health services bill, if it is limited to physical examination and does not include treatment of needs detected by the examination Apparently, almost anything is all right as long as effort is divided, uncoordinated and inefficient, and as long as one does not undertake to do a systematic job in providing health and medical care for the American people Is it that we are afraid of our ability to tackle the real job, or are we afraid of what doing the job successfully would mean? As I have already suggested, should we not rather be afraid of what legislation without considered thought and planning may do?

I do not wish to argue here the pros and cons of the National Health Insurance Act of 1948 (S 1320) vs the National Health Act of 1948 (S 545) But in terms of considered planning vs temporary expediency the two measures may serve as examples

When the original Wagner-Murray-Dingell Bill was first discussed much thought was given to whether medical care should be financed from general tax funds or by application of the insurance principle The more radically inclined favored financing medical care from general tax funds This, they said, applied the principle of progressive taxation and continued the present policy of the rich paying for the medical care of the poor The representatives of labor, however, argued that this was in a sense too socialistic It meant that the lower-income groups would be getting "free medicine" It also meant that most of the public would not directly feel the cost or be aware of it It was argued that application of the insurance principle by payroll deduction was sounder This, it was said, would mean that all labor or gainfully occupied people would be conscious of the cost of the governmentally financed medical care Having visibly paid their money they would insist upon getting their money's worth This would be an excellent check on the economy and efficiency of the services They also emphasized that application of the insurance principle by payroll deduction would automatically designate those whose medicine would have to be financed from general tax funds For obviously all persons against whom payroll deductions were not made would of necessity be needy persons who had to have their medical care paid for by others

The group arguing for application of the insurance principle by payroll deduction won So the Wagner-Murray-Dingell Bill (the National Health Insurance Act of 1948) avoided a "means test" that would be costly in administration and open to all kinds of political pressures at the local administrative levels concerning eligibility Apparently Mr Baruch agrees with this conservative decision by those drawing up the Wagner-Murray-Dingell Bill In the address referred to above, he states

Your [that is, doctors'] organizations have been particularly active in pressing voluntary health insurance You and others have proven group insurance to be a so practical way That is a great achievement. You can be mighty proud of it

But I would not be frank — nor friendly — if I did add what you know It is not good enough

Rome was not doctored in one day It may be, as I have told me, that the needs of the bulk of our people can be met, given time, through voluntary insurance What troubles me most are the needs of that sizable segment of society which does not earn enough to pay for voluntary insurance

Nothing has been suggested so far, which promises success, other than some form of insurance covering the people in by law and financed by the Government, at least in part — what some would call "compulsory health insurance"

As to financing, my own preference runs toward Government meeting only part of the cost, with part coming from payroll deductions from employers and workers.

The detailed problems raised by so-called compulsory health insurance are too numerous to be discussed tonight. I have weighed them most carefully

All law imposes compulsion A form of compulsory health insurance for those who cannot pay for voluntary insurance can be devised, adequately safeguarded, without involving what has been termed "socialized medicine"

Another conservative feature of this bill (S 1320) is its provision for medical education and research. If the people, through their Government, are spending money on medical care, promotion of medical education and research seems highly desirable as a means of maintaining standards and improving the effectiveness of that care In setting aside for education and research 2 per cent of the sums expended on medical care this safeguard seems satisfactorily provided

But just as with the problem of financing medical education, some doctors will have none of this In objecting they have gone to rather extraordinary extremes For example the National Physicians Committee, which is endorsed by the American Medical Association and whose endorsement is now before the Massachusetts Medical Society, spent some \$600,000 last year on propaganda from which the following is taken

THE MOST DEADLY MENACE

Over a period of ten years, no issue in the United States has held the deadly menace that is inherent in the relentless drive to impose on the American people — COMPULSORY HEALTH INSURANCE No other issue has been as assiduously and as persistently promoted by its sponsors

It has taken ten years to unmask the forces behind the sponsorship and to force the issue into the open NOW the sponsors have been unmasked The issue is in the open

The source of the unremitting and relentless drive for Compulsory Health Insurance — Socialized Medicine — is the Political Distribution of Medical Care in this country — is the Moscow dominated Communist Party of the United States

This program did not originate in the United States, but in the secret councils of world communism

The campaign for socialized medicine in the United States stems directly from Kremlin communism

Five years ago similar leaflets of this committee said that the forces behind the sponsorship were Nazism and Hitlerian totalitarianism But apparently that was a mistake However, there appears to be no mistake about Lloyd George, Roose-

affected, whereas in the other family the diagnosis was made in 4 male siblings

CASE REPORT

CASE 1 J W, a 22-year-old Negro, was admitted on January 27, 1947, to the Veterans Administration Hospital, Kecoughtan, Virginia, complaining of constant dull chest pain of 2 months' duration. Concomitant symptoms included exertional dyspnea, occasional hemoptysis and epistaxis. He also complained of weakness, weight loss and fatigue. About 2 weeks prior to admission he had become aware of a diminution of vision and bilateral swelling of the upper eyelids and of the parotid regions. Vague abdominal symptoms became manifest on the week of entry.

The past history was noncontributory. His father was said to have had carcinoma of the stomach.

Physical examination disclosed a well developed and well nourished, ambulant man, who was slightly dyspneic. There were several small, freely movable, nontender, hard nodules palpable in both upper eyelids. The lacrimal glands were enlarged. The mucosa of each nasal passage was hyperemic and excoriated, showing evidence of recent hemorrhages. In the lower portion of the right nasal passage near the vestibule there was a nodule, 2 mm in diameter, that appeared friable. The heart and lungs were essentially normal. There was marked voluntary-muscle spasm and moderate tenderness to palpation in the right upper quadrant. The liver, spleen and kidneys were not palpable. There were no other significant findings.

A roentgenogram of the chest showed a marked degree of symmetrical mottling extending from both hilar regions to the pulmonary periphery. The skull, bones of the hands and wrists showed normal architecture and density. A roentgenogram taken 2 weeks later showed a slight progression in the pulmonary lesion. A gastrointestinal series was normal. An electrocardiogram was within normal limits.

A complete blood count was entirely normal. The urine had a specific gravity of 1.020 and contained a trace of albumin, and an occasional white blood cell was seen in the centrifuged specimen. The blood Wassermann and Kahn tests were negative. The serum protein was 6.3 gm per 100 cc, with 2.7 gm of albumin and 3.6 gm of globulin. The nonprotein nitrogen was 35 mg per 100 cc. A sedimentation rate of 16 mm per hour (Cutler method) was present. The prothrombin time was 21 seconds. Repeated examinations of the sputum for acid-fast bacilli were negative.

The patient was treated with a modified tuberculin regimen consisting primarily of rest and a highly nutritious diet. Because of frequent nosebleeds the nodule in the right nasal passage was removed. There was no return of the epistaxis after this procedure. Microscopical examination revealed one large tubercle composed of epithelioid cells with no caseation or surrounding reaction. The diagnosis was Boeck's sarcoid.

After 2 months of hospitalization he developed a left facial-muscle paralysis which persisted for 4 weeks. The fundi showed bilateral papilledema. A spinal puncture showed normal fluid under a slight increase in pressure. The temperature ranged between 97° and 101°F. An intolerance to salicylates was observed in the course of treatment. There was no regression in the physical findings. However, after sufficient symptomatic improvement, he was discharged after four months in the hospital.

Seven weeks later he returned to the hospital because of an exacerbation of symptoms. He stated that a paralysis of the right side of the face had developed in the interim and that he now suffered almost constant headaches. He had also become aware of some difficulty in speaking.

Physical examination disclosed a dejected and emaciated man with stertorous breathing who constantly expectorated sputum consisting of saliva and streaks of blood. The nodules previously noted on the eyelids persisted. There was mild choking of both disks on funduscopic examination. Auditory perception in the left ear was impaired. The tongue protruded to the right, and a right facial-muscle paralysis was present. Below the angle of the right side of the jaw there were several small, movable, nontender nodules in the subcutaneous tissue. The epitrochlear lymph nodes were enlarged.

The temperature ranged from 97° to 100.2°F and was characterized by an afternoon rise.

A roentgenogram of the lung fields remained unchanged. A film of the sinuses revealed a polyp in the right antrum. An intravenous pyelogram and a barium enema were negative.

The red-cell count and hemoglobin were normal. The white-cell count was 7000, with 60 per cent neutrophils, 36 per cent lymphocytes, 1 per cent monocytes and 3 per cent eosinophils. The sedimentation rate was 20 mm per hour. A urinalysis showed a specific gravity of 1.015 and a trace of albumin. A few white cells and hyaline casts were seen in the sediment. The serum protein totaled 6.6 gm per 100 cc., the serum phosphorus was 3.2 mg, and the alkaline phosphatase 6.6 mg per 100 cc. The serum cholesterol was 264 mg, the blood sugar 87 mg, and the nonprotein nitrogen 30 mg per 100 cc. A urine concentration test showed that the kidneys were unable to concentrate higher than 1.015. Phenolsulfonphthalein kidney-function tests showed 20 to 50 per cent excretion of the dye in 1 hour. First-strength tuberculin — puri-



FIGURE 1 Photomicrograph of Biopsy Specimen in Case 1

fied protein derivative (0.00002 mg) — was negative, whereas second-strength (0.005 mg) was borderline positive.

A specimen for biopsy was taken from an epitrochlear lymph node. Microscopical section showed the node to be composed of nearly confluent tubercles demonstrating epithelioid proliferation with no surrounding reaction, no caseation and no giant cells (Fig 1). The diagnosis was Boeck's sarcoid.

CASE 2 E W, identical twin of J W, entered the Veterans Administration Hospital, Kecoughtan, Virginia, on August 25, 1947, because of a condyloma at the anal orifice.

The past history disclosed that in July, 1945, while in the European Theater of Occupation, the patient had begun to suffer from painful joints, fever and pruritus. He was sent to Ashburn General Hospital, Texas, where lumps appeared in various locations on the body. Weakness, weight loss, cough and periumbilical pains came into prominence. The lacrimal and parotid glands became enlarged. Shortly thereafter a

profession's discouragement of divergent opinion within the profession is unfortunate. Respect in a democracy for minority opinion is perhaps the most conservative way to contribute to the wisdom of majority opinion. Possibly it is this lack of considered debate by the profession that has resulted in its having no constructive program. Again, to quote Dr Park

Granted that it is impossible now to think through the problem of medical care to the very end, it is certainly possible to think a considerable way into it, some requirements are common to any comprehensive medical care plan, and are as evident now as twenty years away. There is no planning in what is going on, and this is because there is no medical leadership.

Its much touted "ten-point program" is no program in any original, dynamic, or constructive sense, or, indeed in any sense, but only a series of pious platitudes.

Its primary concern throughout as judged by its behavior has seemed to me to be aimed consistently at the preservation of the medical care system as it exists today at all costs. Disturbed, it cries out in the words of Fafnir coiled around his treasure, when the youthful Siegfried, the personification of the new order, approaches with his magic sword, "Lass mich schlafen."

In this critical period of change, when the handwriting appears on so many walls, the behavior of organized medicine is humiliating, and its leadership has seemed incredibly stupid.

As a member of the medical profession and the American Medical Association I regret that such criticism can justly be made. It is a serious in-

dictment of the profession. I am often shocked to learn how many physicians have so little information about the matters we are discussing other than what they obtain from the one-sided presentations of the National Physicians Committee and other organizations supporting that point of view. The constructive participation of the medical profession in the development of any national health program is essential for the accomplishment of a good job. Without more adequately financing medical education, research and care a good job cannot be done.

My purpose in speaking tonight is to stress that something is going to be done as remarked by Mr Baruch because of the public's demand, and to urge you as members of the Suffolk District Medical and Massachusetts Medical societies to give considered thought to these matters so that a good job may be done. If not, we as doctors will suffer, as well as the public. I mention specifically this society and the Massachusetts Medical Society not as a politically expedient way of ending comments that may be interpreted by some as unduly critical, but because the past history of both societies amply justifies the expectation that considered thought by you will result in much needed tolerant discussion, intelligent decisions and constructive action.

SARCOIDOSIS IN IDENTICAL TWINS*

JOSEPH F. SHERER, JR., M.D.,† AND ROBERT T. KELLEY, M.D.‡

LITTLE COMPTON, RHODE ISLAND, AND WASHINGTON, D. C.

SINCE the original descriptions by Besnier, Boeck and Schaumann of the disease that now bears their names, many papers¹⁻⁴ have adequately presented the characteristic clinical and pathological findings. However, relatively few authors have reported on the occurrence of sarcoidosis in siblings. No report has been made of sarcoidosis in twins.

Leitner⁵ mentions several authors who have described sarcoidosis as it occurred among members of the same family. He states that Richter found sarcoidosis in sisters. The older one showed involvement of the skin, typical lung findings and splenomegaly, the younger sister had cystic changes in the bones and lesions of the fingers. Dressler observed sarcoidosis in a sister and brother⁶ and in two brothers.⁷ The diagnosis was established on the basis of the clinical picture and roentgenologic findings. MacCormac⁸ described Boeck's sarcoid in sisters aged fifty-four and sixty-one years. In the younger the diagnosis was confirmed by biopsy

as well as typical skin lesions, the appearance of the lungs by roentgenography and a negative Mantoux test. The other sister showed similar lupoid patches, but further studies had not been performed. Bergmann⁹ reports the disease in 2 sisters, with death occurring in each case as a result of right-sided heart failure and chronic hematogenous tuberculosis. In 1 case an autopsy was performed. The other sister was thought to have had the same illness, owing to the strong similarity of the clinical course. Skin lesions of Boeck's sarcoid were seen in both cases. Seller and Berger¹⁰ observed sarcoidosis in 5 siblings in a family of 7, the diagnosis being established by biopsy. Boggild's¹¹ report consists of the findings in sisters, two and five years of age, with roentgenographic evidence of lesions in the bones of the hands that was considered pathognomonic of Boeck's sarcoid. There was no histologic evidence of the condition on biopsy.

The first to report sarcoidosis in siblings in the American literature were Robinson and Hahn.¹² They found Boeck's sarcoid in siblings of two unrelated families. In one family two brothers were

*From the Veterans Administration Hospital Kecoughtan Virginia.

†Resident in urology Lankenau Hospital Philadelphia Pennsylvania.

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This publication aroused great interest among patients and physicians alike, for many it represented the first suggestion that vitamin E was therapeutically effective in heart disease. Later in the same month an editorial in the *Journal of the American Medical Association* urged the need for careful evaluation of any such report.²

Although vitamin E has been under investigation for many years and considerable knowledge has been accumulated regarding its chemical and physical properties,³ little is known about its function. All green plants have demonstrable amounts of the vitamin; it is practically impossible to produce an experimental deficiency in animals if natural foods are present in the diet. Deficiency diets have produced many different types of changes depending upon which animals are used. No studies have been made on human beings.

One of the most striking effects of experimental vitamin E deficiency is the occurrence of muscular dystrophy. Houchin and Smith⁴ noted that many of their rabbits on such diets died suddenly in circulatory collapse, manifesting cardiac dilatation on x-ray study before death. The degree of dystrophy was not sufficient, they believed, to have caused the deaths, which they attributed to cardiac failure. Gullickson and Calverley⁵ were also impressed by the phenomenon of sudden circulatory collapse, and were able to demonstrate electrocardiographic changes of a significant degree in 2 experiments on cattle that died in this manner on diets deficient in vitamin E. Post-mortem examination revealed atrophy and scarring of the heart muscle with an increase in cellular elements, some

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The difficulty of applying these experimental and theoretical considerations to clinical disorders in man is apparent. It is not possible to demonstrate a constant cardiac lesion, the action of the vitamin is not thoroughly understood, and it is extremely unlikely that vitamin E deficiency exists, even in human beings whose diets are far below the usual requirements. Because it is not possible, therefore, to demonstrate vitamin E deficiency as an etiologic factor in heart disease, its use in human beings must be considered largely empirical.

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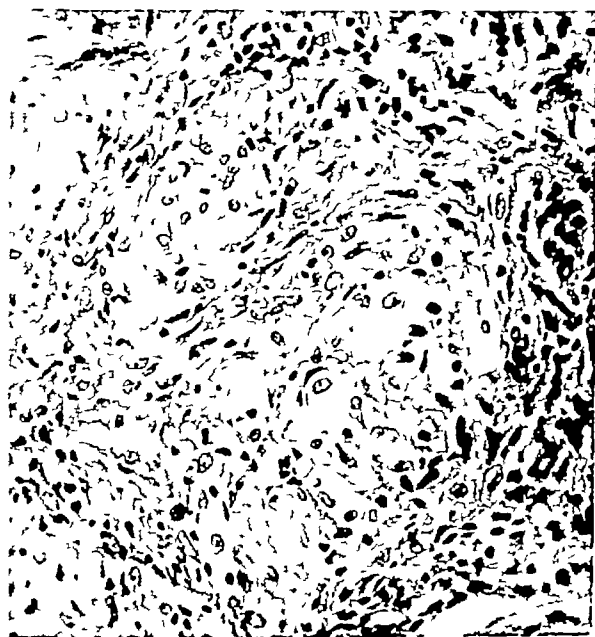


FIGURE 2 Photomicrograph of Biopsy Specimen in Case 2

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A roentgenogram of the chest disclosed the hilar lymph nodes to be moderately enlarged. There was diffuse nodular infiltration extending from the hilar regions into the parenchyma of both lungs. Roentgenograms of the hands, feet and all the long bones of the extremities were normal.

The blood picture was normal. The serum calcium was 11 mg, the phosphorus was 3.6 mg, and the alkaline phosphatase 6.6 mg per 100 cc. The serum protein was 6.6 gm per 100 cc, with 3.6 gm of albumin and 3.0 gm of globulin. The serum cholesterol was 223 gm per 100 cc. The urine concentrated to 1:020. A phenolsulfonephthalein test showed 35 per cent excretion of the dye in 1 hour. No Bence-Jones protein was found.

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menting on his finding of sarcoidosis in siblings, expressed the opinion that the constitution had a significant effect on the pathogenesis of this disease, which he believed was tuberculous in origin. In his first case report he noted that the sister and brother affected with the disease bore a stronger resemblance to each other than to other siblings of the family. This suggests a constitutional predisposition.

Bergmann⁹ also believed that sarcoidosis is a benign atypical form of tuberculosis. He considered the disease to be manifested by a reaction in the form of a generalized hyaline sclerosis on a constitutional basis. He further stated that this form of reaction is in a stage of mutation as a consequence of widespread infection of the general population. One of his points in favor of a constitutional background is the appearance of the disease in siblings. He showed in his report that his patients had other likenesses, such as obesity, that are at times considered to have a constitutional basis.

Robinson and Hahn¹² mentioned the striking similarity in the symptoms and clinical course of the disease in 2 brothers.

In the cases presented above we were impressed by the unusual similarity of the clinical picture of a disease of such protean manifestations. This observation, together with the fact that the patients were identical twins, further indicates a constitutional basis for this disease.

SUMMARY

Two cases of sarcoidosis in identical twins are reported.

The role of the constitutional factor in sarcoidosis is discussed. It is concluded that the constitution may play a significant part in the pathogenesis.

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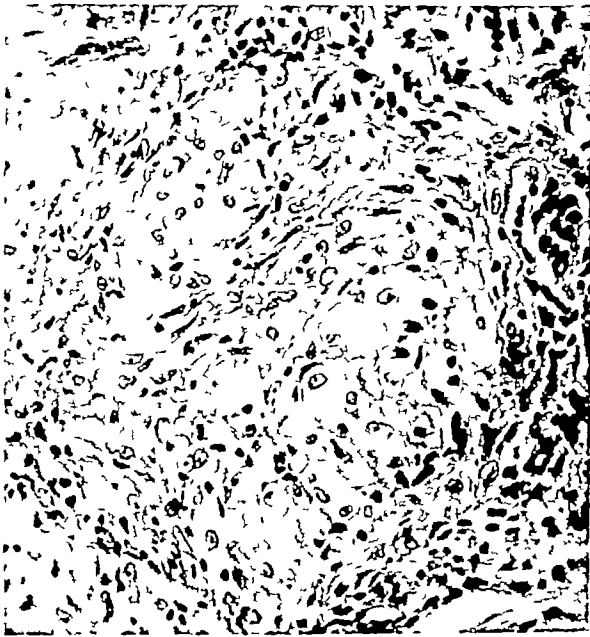


FIGURE 2 Photomicrograph of Biopsy Specimen in Case 2

mass, about 10 cm in its longest diameter, was attached to a pedicle outside the anal mucosa.

A roentgenogram of the chest disclosed the hilar lymph nodes to be moderately enlarged. There was diffuse nodular infiltration extending from the hilar regions into the parenchyma of both lungs. Roentgenograms of the hands, feet and all the long bones of the extremities were normal.

The blood picture was normal. The serum calcium was 11 mg, the phosphorus was 3.6 mg, and the alkaline phosphatase 6.6 mg per 100 cc. The serum protein was 6.6 gm per 100 cc, with 3.6 gm of albumin and 3.0 gm of globulin. The serum cholesterol was 223 gm per 100 cc. The urine concentrated to 1020. A phenolsulfonephthalein test showed 35 per cent excretion of the dye in 1 hour. No Bence-Jones protein was found.

First-strength and second-strength tuberculin (purified protein derivatives) were negative. An electrocardiogram was normal. A specimen of a lesion on the skin was taken for biopsy. On microscopic examination there were subcutaneous tubercles with no reaction caseation or Langhans's cells (Fig. 2). The diagnosis was Boeck's sarcoid.

DISCUSSION

Little has been written regarding the role played by the constitution in sarcoidosis. Dressler,⁶ com-

and rales at both lung bases. No toxicity was evident from the combined use of digitalis and vitamin E.

DISCUSSION

Vitamin E is a mixture of alpha, beta and gamma tocopherols. These may be present in varying proportions. It is claimed that the alpha tocopherol content of vitamin E determines its efficacy in the treatment of heart disease.¹⁰ In no case has it been maintained that the heart disease represented

uniform benefit in as short a period as a few days to a few weeks.

SUMMARY

A small, carefully selected group of patients suffering from angina pectoris were treated with 500 mg of vitamin E (approximately 250 mg of alpha tocopherol) daily. These patients were studied by an exercise-tolerance test, and note was made of any subjective or objective change during the course of treatment, which varied from four to twenty-four

TABLE 1 (Continued)

CASE No	Two-STEP TEST				NITROGLYCERIN TABLETS		DURATION OF TREATMENT	SUBJECTIVE CHANGE	OBJECTIVE CHANGE
	BEFORE TREATMENT		AFTER TREATMENT		BEFORE TREATMENT	AFTER TREATMENT			
	trips	min.	trips	min.	per day	per day	sec		
1	32	5	30	5	7-10	7-10	4	None	None
2	12	2	16	2	20-30	30-40	4	Slight improvement	None
3	12	2½	13	2½	2-5	2-5	24	None	None
4	7	1	4	1	0-1	0-1	24	None	None
5	16	2	14	2	15-20	20-25	24	None	None
6	20	2½	22	2½	5-10	5-10	16	Patient worse	None
7	50	4	50	4	0	0	10	None	None
8	18	3½	17	3	0	0	12	None	None
9	27	2	26	2	0	0	18	Slight improvement	None
10	11	1	12	1	0	0	6	None	None
11	32	3	55	3	0	0	12	None	None

either vitamin E or alpha tocopherol deficiency. Rather, it must be assumed that these substances exert a positive action comparable to other, non-vitamin, drugs in increasing the efficiency of the circulation. For this purpose, it is maintained that doses much larger than those that might otherwise be used are necessary for beneficial results. The alpha tocopherol content of the preparation used in this study was 50 per cent, making the daily dosage 250 mg of alpha tocopherol. This is comparable to the average dosage of the various preparations originally used by the Shutes and their co-workers in their treatment of patients suffering from angina pectoris. The method of assay of the alpha tocopherol content of vitamin E has been criticized by these workers, who maintain that biologic assay is the only reliable procedure. These points remain to be proved conclusively. At present they represent items of possible controversy in attempting to reconcile the results of the present study with those of others who have reported almost

weeks. In only 1 case was there even slight objective benefit.

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a major symptom. Many etiologic types were involved, and all degrees of functional impairment were represented. Eighty-one improved on this therapy, in 52 cases the improvement was noted to be complete or marked. In this series the vitamin E was administered in various forms — in some cases as mixed tocopherols, and in others as alpha tocopherol. Shute states that any capsule containing 50 mg of natural mixed tocopherols has been crudely equated to 25 mg of alpha tocopherol. He has recently observed that the average satis-

tocopherols. Assay of this product has shown it to have an alpha tocopherol content of 50 per cent — which brought the daily dosage of alpha tocopherol to 250 mg. During the course of the investigation, patients were required to avoid the use of mineral oil or cod liver oil, as well as any iron preparations, which Shute believes may inactivate the vitamin.

Table 1 presents the results of the administration of the tocopherols to this group. Eleven patients were accepted for treatment. The etiology of their heart disease was arteriosclerosis or hypertension,

TABLE 1 *Results of Administration of Vitamin E to Patients with Angina Pectoris*

CASE No	AGE	SEX	RACE	DIAGNOSIS	DURATION OF ANGINA PECTORIS
1	yr 70	M	W	Arteriosclerotic heart disease pernicious anemia (treated)	yr 3
2	72	M	W	Arteriosclerotic heart disease angina pectoris decubitus	7
3	51	F	N	Syphilitic heart disease with aortitis diabetes mellitus.	3
4	68	M	W	Arteriosclerotic heart disease diabetes mellitus	3
5	54	M	W	Arteriosclerotic heart disease, angina pectoris decubitus.	5
6	65	M	W	Rheumatic and arteriosclerotic heart disease	10
7	59	M	W	Hypertensive and arteriosclerotic heart disease diabetes mellitus	2
8	60	F	W	Arteriosclerotic heart disease	10
9	60	F	W	Arteriosclerotic heart disease	1
10	58	F	W	Hypertensive and arteriosclerotic heart disease	1½
11	60	F	W	Arteriosclerotic heart disease	10

factory dose is between 200 and 300 mg of alpha tocopherol.¹¹

The present study represents an attempt to evaluate vitamin E therapy on a small, carefully controlled group of patients with angina pectoris as the presenting complaint. The method of evaluation was similar to that described by Riseman and Stern¹² for testing the efficacy of various drugs in angina pectoris by an exercise-tolerance test under controlled conditions. All patients were systematically investigated in the usual fashion with history, physical examination, routine blood counts, blood Hinton test, electrocardiogram and x-ray film of the heart. On three separate occasions, at weekly intervals, they were given the two-step test before being started on vitamin therapy. In this way a base line of performance was established, and the patients were familiarized with the procedure. Each patient was required to rest for an hour before the test, and no nitroglycerin was taken during this time. The patients were rechecked at intervals of two or three weeks after starting treatment, and the performance was recorded. Each patient kept a memorandum of the number of anginal attacks experienced between examinations, and of the number of nitroglycerin tablets used. After suitable control determinations had been made, each patient was given 250 mg of vitamin E, to be taken twice daily, in the form of natural mixed

or both, in 10 cases, and syphilis in 1. The duration of anginal symptoms varied from one to ten years. The duration of treatment ranged from four to twenty-four weeks, the average for the group being fourteen weeks. The columns headed "Before Treatment" represent the average of three two-step tests, and the number of nitroglycerin tablets used daily. The columns headed "After Treatment" represent the performance at the end of the testing period, and the number of nitroglycerin tablets taken at that time. Performances recorded during the testing period closely approximated the figures given for the end of treatment. Subjective changes reflected estimates by the patients of any improvement in feeling of well-being.

In no case except Case 2 was there any difference between the performance before and after treatment, and in this case the consumption of nitroglycerin had increased markedly in the month during which the patient was followed. The patient in Case 9 experienced slight subjective improvement, but there was no improvement in the performance of the two-step test. The patient in Case 3 had been taking digitalis for a year prior to vitamin E treatment. It was necessary to continue this whether or not she was taking the vitamin. When, for a three-week period she was unable to purchase digitalis and omitted its use, she required redigitalization because of the development of severe dyspnea.

and rales at both lung bases. No toxicity was evident from the combined use of digitalis and vitamin E.

Discussion

Vitamin E is a mixture of alpha, beta and gamma tocopherols. These may be present in varying proportions. It is claimed that the alpha tocopherol content of vitamin E determines its efficacy in the treatment of heart disease.¹⁰ In no case has it been maintained that the heart disease represented

uniform benefit in as short a period as a few days to a few weeks.

SUMMARY

A small, carefully selected group of patients suffering from angina pectoris were treated with 500 mg of vitamin E (approximately 250 mg of alpha tocopherol) daily. These patients were studied by an exercise-tolerance test, and note was made of any subjective or objective change during the course of treatment, which varied from four to twenty-four

TABLE 1 (Continued)

CASE No	TWO-STEP TEST				NITROGLYCERIN TABLETS		DURATION OF TREATMENT	SUBJECTIVE CHANGE	OBJECTIVE CHANGE
	BEFORE TREATMENT		AFTER TREATMENT		BEFORE TREATMENT	AFTER TREATMENT			
	trips	min	trips	min	per day	per day	wk		
1	32	5	30	5	7-10	7-10	4	None	None
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4	7	1	4	1	0-1	0-1	24	None	None
5	16	2	14	2	15-20	20-25	24	None	None
6	20	2½	22	2½	5-10	5-10	16	Patient worse	None
7	50	4	50	4	0	0	10	None	None
8	18	3½	17	3	0	0	12	None	None
9	27	2	26	2	0	0	18	Slight improvement	None
10	11	1	12	1	0	0	6	None	None
11	32	3	35	3	0	0	12	None	None

either vitamin E or alpha tocopherol deficiency. Rather, it must be assumed that these substances exert a positive action comparable to other, non-vitamin, drugs in increasing the efficiency of the circulation. For this purpose, it is maintained that doses much larger than those that might otherwise be used are necessary for beneficial results. The alpha tocopherol content of the preparation used in this study was 50 per cent, making the daily dosage 250 mg of alpha tocopherol. This is comparable to the average dosage of the various preparations originally used by the Shutes and their co-workers in their treatment of patients suffering from angina pectoris. The method of assay of the alpha tocopherol content of vitamin E has been criticized by these workers, who maintain that biologic assay is the only reliable procedure. These points remain to be proved conclusively. At present they represent items of possible controversy in attempting to reconcile the results of the present study with those of others who have reported almost

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MONORCHISM*

A Report of Two Cases

GEORGE K. KAWAICHI, M D,† PHILIP COOPER, M D,‡ AND HAROLD F. O'DONNELL, M D§

WICHITA, KANSAS

CONGENITAL absence of one testis or both testes is still considered rare. Since the advent of surgical treatment for "cryptorchidism," however, an increasing number of cases of monorchism or anorchism have been reported. Gruber,¹ in 1878, reviewed the literature for a period of three hundred years and was able to verify only 23 cases of monorchism and 7 cases of anorchism. In the more recent literature, Thorek and Thorek² reported, in 1933, a case of monorchism. Rea,³ in 1938, reviewed the literature and found 40 reported cases of anorchism or monorchism. Of these, 11 were bilateral, and 29 unilateral. He added 6 cases of his own. In 1940, Counseller, Nichols and Smith⁴ reported 7 cases of monorchism. The absence occurred on the left side in 4 and on the right in 3 cases. This brought the number of reported cases of congenital absence of the testes, in the available literature, to 47 cases, 11 being bilateral and 36 unilateral. Because of the importance of bearing in mind that a significant proportion of "cryptorchidism" may actually represent cases of testicular absence and in view of the need of a uniform approach to the problem of monorchism or anorchism, the following cases are presented.

CASE REPORTS

CASE 1. H F S, a 20-year-old man, was admitted to the hospital on April 27, 1949, with a history of an undescended left testis since birth. The patient was admitted by his private physician to have the condition investigated because of the possibility of development of a malignant lesion in an undescended testis.

Physical examination revealed an old, healed right inguinal herniorrhaphy scar. There was a normal testis on the right in proper position. No testis was palpable on the left, but there was a fullness at the left external inguinal ring, suggestive of a testis. Rectal examination revealed a normal prostate. Examinations of the blood and urine were essentially negative. The blood Kahn test was also negative.

On May 3, the left inguinal canal was exposed through the usual herniorrhaphy incision. The spermatic-cord elements, including the vas deferens, were found leading into the scrotum. However, no testis was observed either in the scrotum or the inguinal canal. The cord was followed down to the scrotum, where it ended in a fine ligament. At the end of the vas deferens was a small, soft elongated mass, about 1 cm in length and 3 mm in width. This was excised to the level of the internal inguinal ring. A small indirect hernial sac was found. This was opened, and the peritoneal cavity in this region was inspected and palpated; there was no evidence of a testis. The incision in the skin and muscle was extended, and a meticulous dissection was then made in the

retroperitoneal region as far as the lower pole of the left kidney, but no testis was found. A herniorrhaphy was completed, and the wound closed in the usual manner.

Microscopical sections of the tissues removed from the scrotum revealed atrophic epididymis, in which no spermatozoa were seen, and vas deferens, but no testicular tissue.

CASE 2. C J H, a 29-year-old man, was admitted to the hospital on August 16, 1948, with the diagnosis of a right undescended testis since birth.

Physical examination revealed the left testis to be normal in size and position. The right testis could not be palpated. Rectal examination revealed a normal prostate, and no abnormal masses were palpable. Examinations of the blood and urine, as well as the blood Kahn test, were negative.

On August 23, at exploration through a right inguinal incision, the spermatic cord was found in the usual position leading down into the scrotum, and ending in a ligamentous structure. The vas deferens ended in a few strands of soft tissue, and tissue somewhat suggestive of atrophic epididymis, but no testicular tissue was found. The cord with the attached tissues was removed at the internal inguinal ring. A herniorrhaphy was then done, and the wound closed. The peritoneal cavity was then opened through a right rectus incision, and a careful search was made for an undescended testis. The parietal peritoneum was also incised lateral to the ascending colon and the retroperitoneal area thoroughly searched, but no testis was found. The parietal peritoneum was sutured. A long, chronically inflamed appendix was easily delivered and removed.

Microscopical study of the removed tissue revealed an atrophic vas deferens but no definite epididymis or testicular tissue.

DISCUSSION

Anorchism and monorchism should not be confused with cryptorchidism or with a testis showing clinical evidence of atrophy. Anorchism refers to the absence of both testes and monorchism to the absence of one testis.

The testis develops embryologically from the genital fold, which is essentially part of the mesonephros. The epididymis and the vas deferens develop from elements of the mesonephros. The epididymis and the testis form luminal continuity approximately at the 60-mm stage. One can readily see from this brief review that the close anatomic relation of the epididymis and the testis during development make the possibility of the descent of the epididymis into the scrotum and the retention of the testis in the abdomen very unlikely.

Conceivably, there may be slight separation of the testis from the epididymis and vas deferens. This has been demonstrated by Badenoch,⁵ who reported 3 cases of complete separation of the epididymis and the testis in a series of 42 patients operated upon for cryptorchidism. In the first case, the testis was just below the internal inguinal ring, and the epididymis was found near the external inguinal

*From the Veterans Administration Hospital.
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†Urologist, Veterans Administration Hospital.

‡Chief of surgery, Veterans Administration Hospital.

§Consultant in urology, Veterans Administration Hospital.

ring In the second case, the testis was intra-abdominal but near the internal inguinal ring, and the epididymis was found in the upper part of the scrotum In the last case, the testis was just below the external inguinal ring, and the epididymis was at the bottom of the scrotum

Counseller, Nichols and Smith⁴ also point out that if other parts of the seminal apparatus can be readily located, the presence of a gonad in a remotely aberrant position is unlikely

Lazarus and Marks⁶ reported a case of complete separation of the epididymis and vas deferens and an abdominal testis The epididymis and vas were found in the inguinal canal, and the testicle was found just inside the internal inguinal ring

According to Felix,⁷ an abdominal testis, if present, will be found in the region of the internal inguinal ring

Bremer and Farber⁸ offer the following opinion concerning the absence of a testis with evidence of vas and epididymis in the scrotum

If sections have been taken of the "vas and atrophic epididymis" and the tissues identified as such microscopically, the best possibility in explaining the absent testicle is that primary atrophy of the testis occurred, either during development or later after descent into the scrotum Due to the close anatomic relationships of the epididymis and testis during development, the possibility of their separation with retention of the testis in the canal and descent of the epididymis and vas is very unlikely

This opinion, in conjunction with other reported findings, we believe establishes a logical surgical approach to the problem of anorchism or monorchism

There is some difference of opinion among surgeons regarding what constitutes adequate exploration for an apparent absent testis Some advise

merely exploration of the inguinal canal and scrotum, others advise additional exploration of the retroperitoneal structures It must be admitted that a meticulous retroperitoneal operative dissection may fail to disclose a minute remnant of testicular tissue, but it should reveal a testis of any reasonable size

CONCLUSION

On the basis of this review, it is believed that in the presence of vas deferens, and epididymis in the scrotum, exploration for the testis could be safely limited to exploration of the scrotum, inguinal canal and the peritoneal cavity in the region of the internal inguinal ring

The problem arises whether such a limited procedure can be justified in the presence only of a vas deferens in the scrotum In all probability it is justified, but the absolute justification must await more clinical observations

In the 2 cases reported, primary atrophy of the testis in one and primary atrophy of the testis and epididymis in the other are the most logical explanations for their absence at the time of surgical exploration

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MONORCHISM*

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On May 3, the left inguinal canal was exposed through the usual herniorrhaphy incision. The spermatic-cord elements, including the vas deferens, were found leading into the scrotum. However, no testis was observed either in the scrotum or the inguinal canal. The cord was followed down to the scrotum, where it ended in a fine ligament. At the end of the vas deferens was a small, soft elongated mass, about 1 cm in length and 3 mm in width. This was excised to the level of the internal inguinal ring. A small indirect hernial sac was found. This was opened, and the peritoneal cavity in this region was inspected and palpated; there was no evidence of a testis. The incision in the skin and muscle was extended, and a meticulous dissection was then made in the

retroperitoneal region as far as the lower pole of the left kidney, but no testis was found. A herniorrhaphy was completed, and the wound closed in the usual manner.

Microscopical sections of the tissues removed from the scrotum revealed atrophic epididymis, in which no spermatozoa were seen, and vas deferens, but no testicular tissue.

CASE 2 C. J. H., a 29-year-old man, was admitted to the hospital on August 16, 1948, with the diagnosis of a right undescended testis since birth.

Physical examination revealed the left testis to be normal in size and position. The right testis could not be palpated. Rectal examination revealed a normal prostate, and no abnormal masses were palpable. Examinations of the blood and urine, as well as the blood Kahn test, were negative.

On August 23, at exploration through a right inguinal incision, the spermatic cord was found in the usual position leading down into the scrotum, and ending in a ligamentous structure. The vas deferens ended in a few strands of soft tissue, and tissue somewhat suggestive of atrophic epididymis, but no testicular tissue was found. The cord with the attached tissues was removed at the internal inguinal ring. A herniorrhaphy was then done, and the wound closed. The peritoneal cavity was then opened through a right rectus incision, and a careful search was made for an undescended testis. The parietal peritoneum was also incised lateral to the ascending colon and the retroperitoneal area thoroughly searched, but no testis was found. The parietal peritoneum was sutured. A long, chronically inflamed appendix was easily delivered and removed.

Microscopical study of the removed tissue revealed an atrophic vas deferens but no definite epididymis or testicular tissue.

DISCUSSION

Anorchism and monorchism should not be confused with cryptorchidism or with a testis showing clinical evidence of atrophy. Anorchism refers to the absence of both testes and monorchism to the absence of one testis.

The testis develops embryologically from the genital fold, which is essentially part of the mesonephros. The epididymis and the vas deferens develop from elements of the mesonephros. The epididymis and the testis form luminal continuity approximately at the 60-mm stage. One can readily see from this brief review that the close anatomic relation of the epididymis and the testis during development make the possibility of the descent of the epididymis into the scrotum and the retention of the testis in the abdomen very unlikely.

Conceivably, there may be slight separation of the testis from the epididymis and vas deferens. This has been demonstrated by Badenoch,⁵ who reported 3 cases of complete separation of the epididymis and the testis in a series of 42 patients operated upon for cryptorchidism. In the first case, the testis was just below the internal inguinal ring, and the epididymis was found near the external inguinal

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†Urologist, Veterans Administration Hospital.

‡Chief of surgery, Veterans Administration Hospital.

§Consultant in urology, Veterans Administration Hospital.

ring In the second case, the testis was intra-abdominal but near the internal inguinal ring, and the epididymis was found in the upper part of the scrotum In the last case, the testis was just below the external inguinal ring, and the epididymis was at the bottom of the scrotum

Counseller, Nichols and Smith⁴ also point out that if other parts of the seminal apparatus can be readily located, the presence of a gonad in a remotely aberrant position is unlikely

Lazarus and Marks⁶ reported a case of complete separation of the epididymis and vas deferens and an abdominal testis The epididymis and vas were found in the inguinal canal, and the testicle was found just inside the internal inguinal ring

According to Felix,⁷ an abdominal testis, if present, will be found in the region of the internal inguinal ring

Bremer and Farber⁸ offer the following opinion concerning the absence of a testis with evidence of vas and epididymis in the scrotum

If sections have been taken of the "vas and atrophic epididymis" and the tissues identified as such microscopically, the best possibility in explaining the absent testicle is that primary atrophy of the testis occurred, either during development or later after descent into the scrotum Due to the close anatomic relationships of the epididymis and testis during development, the possibility of their separation with retention of the testis in the canal and descent of the epididymis and vas is very unlikely

This opinion, in conjunction with other reported findings, we believe establishes a logical surgical approach to the problem of anorchism or monorchism

There is some difference of opinion among surgeons regarding what constitutes adequate exploration for an apparent absent testis Some advise

merely exploration of the inguinal canal and scrotum, others advise additional exploration of the retroperitoneal structures It must be admitted that a meticulous retroperitoneal operative dissection may fail to disclose a minute remnant of testicular tissue, but it should reveal a testis of any reasonable size

CONCLUSION

On the basis of this review, it is believed that in the presence of vas deferens, and epididymis in the scrotum, exploration for the testis could be safely limited to exploration of the scrotum, inguinal canal and the peritoneal cavity in the region of the internal inguinal ring

The problem arises whether such a limited procedure can be justified in the presence only of a vas deferens in the scrotum In all probability it is justified, but the absolute justification must await more clinical observations

In the 2 cases reported, primary atrophy of the testis in one and primary atrophy of the testis and epididymis in the other are the most logical explanations for their absence at the time of surgical exploration

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MONORCHISM*

A Report of Two Cases

GEORGE K. KAWAICHI, M.D.,† PHILIP COOPER, M.D.,‡ AND HAROLD F. O'DONNELL, M.D.§

WICHITA, KANSAS

CONGENITAL absence of one testis or both testes is still considered rare. Since the advent of surgical treatment for "cryptorchidism," however, an increasing number of cases of monorchism or anorchism have been reported. Gruber,¹ in 1878, reviewed the literature for a period of three hundred years and was able to verify only 23 cases of monorchism and 7 cases of anorchism. In the more recent literature, Thorek and Thorek² reported, in 1933, a case of monorchism. Rea,³ in 1938, reviewed the literature and found 40 reported cases of anorchism or monorchism. Of these, 11 were bilateral, and 29 unilateral. He added 6 cases of his own. In 1940, Counsellor, Nichols and Smith⁴ reported 7 cases of monorchism. The absence occurred on the left side in 4 and on the right in 3 cases. This brought the number of reported cases of congenital absence of the testes, in the available literature, to 47 cases, 11 being bilateral and 36 unilateral. Because of the importance of bearing in mind that a significant proportion of "cryptorchidism" may actually represent cases of testicular absence and in view of the need of a uniform approach to the problem of monorchism or anorchism, the following cases are presented.

CASE REPORTS

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retroperitoneal region as far as the lower pole of the left kidney, but no testis was found. A herniorrhaphy was completed, and the wound closed in the usual manner.

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Holman⁷⁷ reports on the use of trichophytin in thromboangitis obliterans. Ninety-three per cent of these patients had clinical trichophytosis compared with only 73 per cent of the control patients. Four times as many patients with this disease had positive trichophytin tests as the controls did. This paper suggests a more thorough trial of trichophytin in cases of thromboangitis obliterans.

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INFECTION

Dodd et al⁷⁹ report 88 cases of aphthous stomatitis in children up to fourteen years of age. The type of stomatitis described is a definite clinical entity with the virus of herpes simplex as the causative factor. It is probable that the disease represents a primary herpetic infection.

Burnet and Williams⁸⁰ also conclude that aphthous stomatitis in infants is the primary herpetic infection. They believe that once infection has begun the virus of herpes simplex remains in the body for life, showing activity under a suitable stimulus such as fever or trauma. The article states that in childhood a nonspecific resistance to the primary infection develops. When this stage is reached, the population is permanently divided into two groups—herpetic and nonherpetic. In the former, the virus persists, occasionally manifesting itself by lesions and by supplying a constant or intermittent antigen stimulus to maintain antibodies at high level. The nonherpetic patient is exposed but, owing to development of resistance, goes unscathed. In conclusion Burnet and Williams state that the herpes virus is probably the only virus that lives an almost symbiotic existence in man. Herpes simplex can be a very annoying and disfiguring affliction when it recurs frequently. It may appear monthly in highly susceptible persons.

Nagler⁸¹ summarizes his article on herpes simplex by stating that when a heated inactivated preparation of herpes simplex virus is inoculated intracutaneously in herpetic persons, a specific erythematous reaction is produced. A positive intracutaneous reaction is regularly correlated with the presence of circulating antibodies against herpes virus. In a later article he⁸² states that a herpes simplex skin-test reagent prepared from infected amniotic fluids has been shown to be easier to prepare, to contain only a trace of nonspecific protein and to give more specific results than a chorioallantoic reagent previously used.

Leff⁸³ reports a forty-four-year-old patient with herpes zoster of the right side of the chest and the Ramsay-Hunt syndrome—left-facial-muscle paralysis, decreased pain sensation over the left side of the face in all three divisions, absent left corneal reflex, loss of taste over two thirds of the left side of the tongue, moderate deafness of the left ear, vesicular eruption on the left anterior faucial pillar and decreased sensation in the left external auditory canal. These clinical findings confirm the current opinion that the Ramsay-Hunt syndrome is not geniculate ganglionitis alone but rather a concurrent involvement of several cranial nerves.

According to Mandelbaum and Hollander,⁸⁴ the diagnosis of Brill's disease (American typhus fever) may be established by biopsy. They find that rickettsial diseases produce vasculitis and perivasculitis. Rickettsias may also be found in the biopsy specimen. The dependability of the biopsy in diagnosis must be confirmed.

Reporting on Kaposi's varicelliform eruption, Unger⁸⁵ states that the disease has been proved to be herpes simplex superimposed on a previous skin disease. In 1944 Brunsting and Barton reported 67 cases, 79 per cent having had atopic dermatitis.

In a comprehensive review of Kaposi's varicelliform eruption, Ruchman⁸⁶ reports 4 cases. He states that of 96 reported cases, 75 were in children. The death rate was 23 per cent in infants and 9 per cent in adults, this is probably higher than the average, for milder cases were probably not reported frequently. Three adults and 1 child (fourteen months old) are discussed in Ruchman's paper. All had an atopic background and had been exposed to herpes simplex for periods of five to ten days, and none to vaccinia. One patient died of respiratory failure after leukopenia developed with fever and disorientation.

Allison and Hobbs⁸⁷ state that "epidemic strains" of *Staphylococcus pyogenes* are usually responsible for pemphigus neonatorum, which is frequently accompanied by staphylococcal conjunctivitis. The most probable course of infection is via the nose and hands of the nurse to the infant's skin, but infants' bath and towels may be important links. Prevention of infection probably depends on exclusion of heavy nasal or skin carriers of *Staphylococcus pyogenes* from the nursery and observation of meticulous preventive measures in the nursery. When all hospitals exclude the use of mercury compounds as preventives against impetigo of the newborn and for antiseptic measures, the incidence of dermatitis and diarrhea among these infants will be much less.

Two American soldiers from the same community in the United States who were tattooed on the same day by the same operator in Melbourne, Australia, developed tuberculoid leprosy in these areas about two and a half years later. One patient

MEDICAL PROGRESS

DERMATOLOGY (Concluded)

JOHN G. DOWNING, M.D.*

BOSTON

BLOOD

Mycosis fungoides fortunately is a comparatively rare disease. Hence, there are a limited number of cases in the various reports on therapy. Henstell⁶⁸ reports that, irrespective of the stage, 6 cases responded immediately to nitrogen mustard. All were radioresistant. Cases with a prolonged premycotic stage showed the best response. In my opinion most follow-up examinations have shown that the improvement has been temporary.

Law⁶⁹ states that tumor formation in mice with transplanted leukemia responded favorably to urethane.

In a paper on the treatment of neoplastic disease with nitrogen mustard, Taffel⁷⁰ reports the results of 16 cases (6 cases of Hodgkin's disease, 2 of stem-cell lymphoma, and 1 each of eight other neoplastic diseases). Six doses of 0.1 mg per kilogram of body weight was given daily, later this was reduced to four doses, and in some cases to 0.05 mg per kilogram. Four patients, 2 of whom had Hodgkin's disease, were given two courses of treatment, so that twenty courses were given in all. No one of the patients was cured, and 10 died (treatment was given within the last three years). The 6 patients still living are far from cured. Although Hodgkin's disease seemed most susceptible to the drug, there was not enough improvement to delay death appreciably. One case of mycosis fungoides was substantially improved, thus far for five months. Taffel comments that the drug is toxic, depresses blood elements and may cause alarming agranulocytic leukopenia and thrombocytopenia. He concludes that in his clinic radiotherapy is preferred for these diseases if the disease is localized, nitrogen mustard is reserved for patients with diffuse systemic involvement and those who have become resistant to x-ray therapy.

Pincoffs⁷¹ summarizes the therapeutic use of nitrogen mustard. He states that reports of 150 cases of different authors treating Hodgkin's disease, lymphosarcoma, chronic leukemia, polycythemia vera, multiple myeloma and a few other neoplasms indicate that nitrogen mustard deserves a subsidiary position in the treatment of the first two diseases and possibly some cases of chronic leukemia. Pincoffs states that more investigation is indicated. He believes that irradiation, as long as it is effective, is the treatment of choice.

Green⁷² treated 2 cases of mycosis fungoides with thorium X, 2000 units in isopropyl alcohol. It was

painted on small affected areas of the skin weekly for six weeks. Erythema and itching were relieved after the first application, but recurred in a few weeks. Subsequently, 100 units of thorium X in saline solution was given intravenously weekly for twelve weeks, with some relief. The blood showed no change after the injections. Again, the local areas were treated with twelve weekly paintings. Four weeks after the last application, the painted areas showed marked decrease or absence of erythema, and the itching was completely relieved. The tumor and ulcer when painted also showed definite improvement.

A six-year clinical evaluation of internal radiation therapy with radioactive phosphorus (P32) is given by Doon et al.,⁷³ who state that this isotope has the greatest value in polycythemia vera. It is a valuable adjunct in chronic leukemias that are intolerant or resistant to roentgen radiation, but has frequently accentuated the acute leukemias. It has failed to control Hodgkin's disease and may threaten the integrity of the bone marrow. Deep bone pain from metastatic cancers may be relieved, but it is doubtful if metastases are retarded. Pruritus in these cases has been controlled at times. Multiple myeloma, mycosis fungoides, metastases to bone and exfoliating dermatitides were not basically improved.

In a report on the effect of rutin on the permeability of cutaneous capillaries, Ambrose and DeEds⁷⁴ state that previous experiments showed rutin (vitamin P) to have no protective action against capillary fragility. Capillary permeability is determined by the injection of trypan blue intravenously, followed by irritation of the skin with chloroform or histamine. Rutin was injected intravenously in 22 rabbits that were irritated by chloroform. In doses of 100 to 200 mg per kilogram of body weight it decreased capillary permeability under the conditions of this test.

Colloidal gold containing the radioactive isotope Au 198 has been suggested for the treatment of diseases of the lymphoid system. In view of the dermatitis-producing factor of gold, this drug should be used carefully when there is a cutaneous manifestation.⁷⁵

Holley⁷⁶ reports 12 cases of agranulocytosis following intensive arsenotherapy treated with BAL. After discontinuance of the arsenic, BAL was given, in conjunction with considerable therapy, such as transfusions and penicillin. The early treatment of these cases with intensive supportive therapy, the inconclusive diagnoses and the early administra-

*Professor of dermatology and syphilology Tufts College Medical School professor of dermatology Boston University School of Medicine

tion of BAL make it difficult to determine how much credit to give the drug for recovery

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had multiple tattoos elsewhere, but these areas produced no leprosy.⁸⁸

Dunham et al.⁸⁹ isolated from a patient with Reiter's disease a filtrable agent that was pathogenic for mice.

Church and Mason⁹⁰ report 10 cases of cutaneous diphtheria occurring in American soldiers in Germany during an epidemic. The diagnosis was made by culture. In 3 cases the foot and leg, in the same number the hands or arm, and in 2 the lower abdomen and the genitalia were involved.

Cutaneous diphtheria simulating lymphopathia venereum and ectodermosis erosiva pluriorificialis has been described by Reiss.⁹¹

Miller and his associates⁹² report the following types of cutaneous and mucomembranous lesions in histoplasmosis: ulceration and granulomas—oval, small, discrete, gray-domed nodules, papules, plaques and punched-out ulcers, purpuric lesions, abscesses, furunculosis and impetiginized areas on the scalp, chest and back and generalized, and dermatitis, local or generalized. They present a comprehensive study and report a case of histoplasmosis in a thirty-seven-year-old laborer who six years previously had received x-ray therapy for what was diagnosed Hodgkin's disease. This is a complete consideration of the subject, with an interesting discussion of the possible relation to reticuloendothelial neoplasms. The discussion showed that many cases were being seen but not reported.

Histoplasmosis is apparently more readily recognized, owing to the copious literature. Martz⁹³ reports the case of a three-year-old girl who was malnourished. She had contracted pertussis a year previously, followed by an unexplained fever and loss of weight. Later symptoms were diarrhea, bleeding lips, gums and fingernails, ecchymosis and lymphadenopathy. An excised lymph node showed histoplasmosis. The patient was hospitalized, but died five days later. Autopsy showed the intestinal tract with its lymph nodes to be particularly involved and harboring numerous histoplasma organisms. This disease is usually found predominantly in the gastrointestinal tract or the respiratory organs, and it is believed that this suggests the mode of entry. The histoplasmin skin test is not dependable as a diagnostic measure.

In an article on histoplasmin and tuberculin reactions in university freshmen, Prior and Allen⁹⁴ report histoplasmin in 75.8 per cent in the southwestern part of the country, as compared to 16.8 per cent in the northeastern section. They found no similar geographic difference existing for tuberculin reactors. Histoplasmosis is probably related to the soil, possibly in the way that coccidioides is related to it.

Disseminated ulcerating sporotrichosis with visceral involvement occurred in a sixty-seven-year-old man. There was painful swelling in the knee,

followed six weeks later by a generalized papular eruption without fever. Biopsy showed a tuberculoid reaction, the lymph nodes were normal. The patient's condition was generally good for five weeks after the appearance of the papules, but he suddenly became worse and died in five days. Autopsy showed *Sporotrichum schenckii* in the skin lesions, spleen, liver, bones and so forth.⁹⁵

The common contaminant, aspergillus, is usually saprophytic, but may be pathogenic under certain conditions. Cawley⁹⁶ reports a fatal case in a child seven and a half years of age. Post-mortem examination showed multiple abscesses in various organs. *Aspergillus fumigatus* was cultured from all lesions.

Baer and Muskatblit⁹⁷ report the case of a twenty-four-year-old man with an eruption on the palms and soles since birth, and on the body and extremities since the age of fourteen. It was diagnosed as erythroderma ichthiosiforme congenitale, but scrapings from the hands, feet, thighs, abdomen, chest and back showed positive cultures for *Trichophyton purpureum*, and the patient was treated accordingly. As stated above, generalized fungous infections may occur in persons with congenital cutaneous dystrophy. The terrain is ideal for fungous growth.

Suppurative ringworm contracted from cattle is reported by Fowle and Georg.⁹⁸ Clinically, it consisted of deep suppurative lesions of the bearded area, kerion lesions of the bearded area and scalp and agminate folliculitis of the glabrous skin.

Wolf⁹⁹ states that at least fifty-three different species of fungi have been reported in the literature as causative of otomycosis. Some were known pathogens, others were not. Most of these fungi are nonpathogens and usually associated with bacteria, and it is not known which is responsible for the otitis. Many so-called cases of otomycosis are merely a seborrheal dermatitis with secondary invasion of nonpathogenic fungi, or pseudomonas organisms.

A case of mucormycosis of the central nervous system associated with hemochromatosis is reported by LeCompte and Meissner.¹⁰⁰ The diagnosis was made from autopsy sections (not cultured).

Sheldon and Heyman¹⁰¹ present histologic studies of 8 cases of lymphogranuloma venereum proved by isolation and identification of the virus. The picture of all three lesions is identical, consisting chiefly of perivascular large mononuclear infiltration, which with some plasma cells and few giant cells obliterates some swollen blood vessels, producing necrosis, polymorphonuclear leukocytes then invade and produce abscesses. The authors believe that the histologic picture is sufficiently distinct to warrant biopsy as a diagnostic procedure in suspected lymphogranuloma venereum.

Glass¹⁰² reports that the hairs and spores from tinea capitis due to *M. audouinii* and *M. lanosum*

are infectious up to one year in 85 per cent and 10 per cent of the cases, respectively

Neves and Costa¹⁰³ define tinea nigra as a contagious, inoculable and autoinoculable dermatomycosis caused by *Cladosporium mansonii* and *C. werneckii*. The clinical characteristics are black or brown pigmentation on the trunk, neck and palms

Muskatblit¹⁰⁴ states that in primary actinomycosis of the skin the probable portal of entry in his case was a carious left lower molar. Normal persons may have pathogenic actinomycetes that are carried by the lymphatics in and around carious teeth. Penicillin is more rapidly effective than the sulfonamides

Two cases of chromoblastomycosis in Panama, diagnosed by sclerotic cells on direct culture of scabs or agglutination, are reported by Calero¹⁰⁵. A good result was obtained in one case with 1200 r filtered through 2 mm of copper and 1 mm of aluminum. In the other case electrocautery was followed by 1000 r

Bernhardt¹⁰⁶ reports dermatophytosis of the face caused by *T. camerounense*. It was the first isolation in America and the first from a human lesion. The patient was seen at the Skin Clinic of the Boston City Hospital

Inflammatory plaques on the lower legs are a common complication of dermatophytosis according to Waisman¹⁰⁷. They are thought to be caused by lymphatic transmission of hemolytic streptococci through fissures on the soles. The question is raised whether they might not be due to fungus toxins. Such cases are uncommon

Muskatblit¹⁰⁸ reports the case of a woman with an itchy eruption on the left foot of four months' duration, this was followed by an eruption on both hands. Scrapings from the fingers were negative, and those from the left sole positive. Cultures showed two colonies: one of these was *T. interdigitale*, white, downy with irregular folds, grooves and convolution, the other was identified as *T. rubrum*, an elevated center with a pinkish down, a flat yellow and powdery middle zone and a peripheral fringe of submerged rays, powdery on the surface and deep red on transillumination

In a report of primary onychomycosis due to aspergillus, Bereston and Waring¹⁰⁹ cultured many colonies of *Aspergillus flavus* and no other fungi. The nail had a dull-green color

Michelson¹¹⁰ treated 6 cases of cutaneous tuberculosis (2 with lupus vulgaris, 1 with tuberculosis colliquativa and 3 with erythema induratum) with viosterol in oil, 150,000 units, and a quart of milk daily. Under treatment for two to five months, all cases were improved, though none were cured

Sagher and Miterstein¹¹¹ report 6 cases of leprosy of the anterior portion of the eyeball treated with Grenz rays. Relief from pain and arrest of the leprosy process were noted in the majority of cases

However, 1 case seemed adversely affected by the radiation

In 1942 herpes simplex (febrilis) was cured within a few days by the internal administration of gynergen (4 to 6 mg of ergotamine tartrate daily) and daily local application of gynergen solutions. Excellent results have been obtained for the neuralgic symptoms of herpes zoster, with disappearance of cutaneous lesions, with daily intravenous injections of gynergen in 0.5-cc doses. Improvement was noted after the third or fourth injection, and medication was then discontinued¹¹². The danger of vascular accidents after the use of ergot or its compounds caused the discontinuance of this drug in dermatology over forty years ago

Three cases of anthrax responded to penicillin therapy, and the patients recovered without incident¹¹³

DDT in various combinations has been recommended for parasitic diseases, including scabies. Various proprietary preparations are warmly advocated^{114, 115}

Hexamidine (a new antiseptic) in 1:1000 hydroalcoholic solution was used in impetigo and the pyodermas, with cure in three to five days without the addition of antiseptic ointments¹¹⁶

According to Cormia and Alsever¹¹⁷ penicillin is a valuable adjunct in pyoderma, but it should not be used without a prior sensitivity test. It is best given in a water-soluble ointment base following hot boric acid packs and opening of the pustules. A concentration of 500 units per gram of ointment is adequate when the causative organisms are sensitive to penicillin. When they are sensitive to penicillin, but only in greater concentrations, the amount of penicillin in the ointment must be increased. Supplementary therapy with sulfonamides has been of limited value

Dermacid, consisting of 6 per cent of sulfacetamide (albicid) in a vanishing-cream base, is recommended in the treatment of multiple septic sores and spots, impetigo, septic abrasions and folliculitis barbae¹¹⁸

Nascent iodine in the form of iodoform (after cleaning and drying of the lesion) or a 10 per cent solution of sodium iodate is suggested in the treatment of tropical ulcers¹¹⁹

When aspergillus extract was deprived of known bacteriostatic or antitoxic properties and injected subcutaneously in a man suffering from a staphylococcal infection, the lesions were decongested within twenty-four hours¹²⁰

In the treatment of carate (pinta), injections of 1,200,000 units of penicillin caused disappearance of the treponemas and the erythema on the arms of the patient¹²¹

Penicillin in peanut oil and beeswax is apparently the method of choice in the treatment of yaws¹²². At least 1,200,000 units is necessary for an adult, the dose being graded according to age. Ninety-

one per cent of those treated showed apparent cure or satisfactory progress.¹²³ Penicillin is apparently the ideal treatment for the early stages, subsequent prolonged arsenical treatment may be necessary in resistant infections.

Willcox et al.¹²⁴ report gold salts as a curative in 2 patients with Reiter's syndrome not associated with bacillary dysentery.

Antimony is recommended for the treatment of American cutaneous leishmaniasis.¹²⁵

Streptomycin was effective in 3 cases of granuloma inguinale reported by Barton and his associates.¹²⁶ The authors lamented the fact that they did not have available sufficient streptomycin to treat these cases sufficiently.

A Negro suffering from sporotrichosis was treated with iontophoresis, with a strong solution of iodine (USP) used in 1:100 dilution at the start and concentrated to 1:50 over a period of three months. Treatments were given for twenty to thirty minutes, five days a week. Improvement was noticed after two weeks' treatment and continued until a cure was obtained.¹²⁷

Iontophoresis with formaldehyde and copper sulfate has been found useful in the treatment of dermatophytosis and hyperhidrosis.¹²⁸ The danger of formaldehyde is its sensitizing properties.

A 1 per cent solution of zinc chloride is deemed unsatisfactory in superficial mycotic infections, except in crural dermatoses and in tinea glabrosa, in which its use seems promising. In this same report, Dolce and Nickerson¹²⁹ found proper foot hygiene and the wearing of sandals instead of "GI" shoes of value in relieving mycotic infections.

Kirby and McNaught¹³⁰ recommend that patients with actinomycosis due to the aerobic *Nocardia asteroides* (*Actinomyces asteroides*) be treated with sulfonamide compounds and penicillin as vigorously as those infected with the anaerobic *Actinomyces bovis* and also that surgical drainage, iodides and roentgen-ray therapy be used as indicated. Generally the aerobic *N. asteroides* responds to sulfonamides, and the anaerobic *A. bovis* responds to penicillin.

In a report on fungicidal and fungistatic properties in vitro of clavacin (a filtrate of *A. clavatus*) on dermatophytes the results varied with the pH of the filtrate, the potency of the filtrate and the time of contact between the test fungi and the filtrate. Organisms found susceptible were, in order of susceptibility *Epidermophyton floccosum*, *T. violaceum*, *M. audouinii*, *T. rubrum*, *M. lanosum* and *T. gypseum*.¹³¹

According to Hopkins,¹³² undecylenic acid and dinitro-cyclohexylphenol gave the highest percentage of clinical successes in dermatophytoses of the feet. The former was believed to be the best for subacute cases. Undecylenic acid, propionic acid and benzoic acid were the least irritating.

Muskatblit¹³³ reports undecylenic acid as a good fungicide, but no better than others. He found no irritation, even in the acute phases.

The claim is made that sodium caprylate ointment (10 per cent), having no sensitizing action and relieving irritation even in denuded areas, is excellent for dermatomycosis of the feet.¹³⁴

In a 400-man ground crew unit of the Royal Air Force in the Netherlands East Indies, the incidence of ringworm of the feet and body was dramatically reduced by a few simple prophylactic measures. Jolly¹³⁵ states that the men wore clean cotton underpants daily, used special, clean foot towels and wore wooden clogs, with a single canvas strap, at all times. A minimum amount of foot powder was used between the toes after drying the skin. The lesions on the body were treated with 1 per cent chrysarobin in Lassar's paste, and the facial lesions with Whitfield's ointment. Brilliant green (1:500 in alcohol) with 3 per cent salicylic acid was used between the toes. The incidence of new cases dropped from 41 at the beginning of the experiment to 2 or 3 a month by the end of the experimental period.

Undecylenic and propionic acids in the prevention and treatment of dermatophytosis are listed by Sulzberger and Kanof¹³⁶ in order of efficacy as follows: undecylenic acid — undecylenate powder, diodoquin — 5 per cent talc, vioform — 1 to 3 per cent in talc, calcium zinc propionate powder, sodium propionate powder, United States Navy foot powder, boric-salicylic acid powder, talcum powder, and thiourea, 5 per cent in talc.

Tinea capitis due to *M. audouinii* was treated with 10 per cent copper undecylenate or 5 per cent salicylanilic ointment or both.¹³⁷ Irradiation is still recommended as the treatment of choice in tinea capitis.¹³⁸ Considering the risk in the hands of most operators, this treatment should be performed only by a dermatologist, or roentgenologist, specially trained for this type of therapy.

A thorough consideration of the entire study of fatty acids (of sweat) as fungicides and fungistatics is reported by Peck and Russ.¹³⁹ Caprylic and propionic fatty acids (of sweat) were combined and their effect in vitro and vivo on fungi and fungous infections of the scalp, pubis, anus, nails, hands and feet was observed. This mixture was superior in vitro to other fatty acids of sweat, and appeared more effective than any other fatty acids tried for these diseases. The ideal fungicide and curative agent for fungous infections of the skin has not yet been discovered. The fatty acids are very promising, their chief advantage being that they are for the most part nonirritating and do not sensitize. As to their curative powers, there seems to be a discrepancy in the various reports of investigators.

Studying fungicides for vaginal moniliasis, Hessel-tine¹⁴⁰ found that the most promising were ricinoleic

acid and three forms of cetyl ammonium chloride, all of which were completely fungistatic

Kendall¹⁴¹ reports the treatment of monilial vulvovaginitis with tap-water douche followed by 2.5 per cent undecylenic acid and 10 per cent zinc undecylenate in a base of equal parts of vanishing cream and lubricating jelly (desenex ointment). It is a simple nonstaining treatment.

Glycerite of hydrogen peroxide acts on organisms resistant to penicillin. Its use in the treatment of otitis externa seems justified.¹⁴²

SCLEROSSES

Two interesting cases of periarteritis nodosa show the value of biopsies in diseases in which physical signs are too variable to establish a diagnosis. The first patient presented a quiescent pulmonary tuberculosis, but active tuberculous lymph nodes in the neck. With each attack of fever, nodules characteristic of periarteritis nodosa appeared, suggesting a tuberculous antigen as the etiologic factor for the skin nodules. The patient recovered. The other patient, with no history of sensitization or skin lesions, died within a year of periarteritis involving the abdominal organs, muscles, brain and kidneys.¹⁴³

In view of the tendency to attribute various common inflammatory reactions to anaphylaxis, the thorough work of Goddard¹⁴⁴ is of more than academic interest. Using sensitized guinea pigs he showed that granulomas resulting from anaphylaxis have more histiocytes and eosinophils, with giant cells, than inflammatory granulomas — that is, they are quantitatively and qualitatively different.

In an experiment with rutin, Raiman et al.¹⁴⁵ found that it protects guinea pigs against anaphylactic shock but not against histamine shock.

Wuerthele¹⁴⁶ reports a case of scleroderma treated with promin. A 5 per cent jelly was applied three times daily, and in three months the patient was able to return to work.

Presenting a case of sclerema adiposum neonatorum (proved by biopsy), Sternbach and Robinson¹⁴⁷ discuss the distinction between this disease, scleredema neonatorum and pseudosclerema (subcutaneous fat necrosis). Sixteen hours after birth the baby developed clonus of the facial and arm muscles, on the second day there was spasticity of all the extremities, cyanosis and regurgitation. Four days later there was thrush and a hard subcutaneous mass in the left arm, followed by a scalp infection with gangrenous slough over the occiput. Twelve days after birth there were many hard subcutaneous nodules over most of the body, and the patient died at sixty-four days. Autopsy showed a typical skin picture. The other organs were normal except for the liver, which showed cloudy swelling and hydropic degeneration.

Liebow and Feil¹⁴⁸ found that in lupus erythematosus disseminatus, electrocardiographic abnormalities were noted as long as ten months before death and that they became progressively more abnormal. This report shows the frequency with which the myocardium is attacked by lupus erythematosus.

Thirty cases of lupus erythematosus (chiefly the chronic discoid type) were treated by Schmidt¹⁴⁹ with nicotinic acid by mouth and gold intramuscularly and intravenously. The dosage for the nicotinic acid was 50 to 100 mg orally after meals. Smoking and other habits that might produce vasoconstriction were restricted. The dosage of gold sulfide is graduated from 2.0 to 5.0 cc every five days.

NEW GROWTHS

Woodburne¹⁵⁰ reports that synovial cysts, ganglions and the like were best treated with x-ray therapy — 150 KV 3 mm al., two doses of 500 r each in one week. Slight atrophy occurred with this treatment, but this according to the author may have to be accepted if symptoms warrant the treatment. In my opinion surgery produces better results.

From England comes the report of a rare disease, keratoderma punctata, by Phillips.¹⁵¹ The patient, a thirty-two-year-old man, gave a history of small hard lumps on the creases of the palms and inner borders of the feet, the symptoms having developed three months previously. The plugs remained about a week and dropped out, and new ones developed.

According to Drucker,¹⁵² the results of the treatment of 37 cases of hemangioendothelioma indicate that surgical excision and irradiation offer the best therapy. The etiology is indefinite, but the disease is often considered as being due to trauma, evolving from hemangioma to the malignant form hemangioendothelioma. Metastasis occurs through the blood stream and sometimes through the lymphatics, and tends to recur after surgery.

From Australia comes a report on a new method of treating capillary hemangiomas by tattoo with titanium or zinc oxide, with the occasional addition of mercury sulfide (red) or hydrated chrome oxide (green) to adjust the color. The tattoo material is deposited between the capillary bed and the basal-cell layer, thereby permitting the pigment of the latter to give its natural color to the skin. Seven patients thus treated were satisfied with the cosmetic result.¹⁵³

Miller et al.¹⁵⁴ present an article on the general consideration of leukoplakia of the vulva. One hundred and forty-three cases were studied, including the hypertrophic and the atrophic krauroses. Careful studies revealed no valuable etiologic findings. Although the authors offer no substitute for surgery, they appear rather too critical of it. They consider that surgical excision may have to be used for symptomatic relief, but vulvectomy is an imperfect sub-

stitute for a medical cure, which, it is hoped, some day will be available. However, they strongly advocate radical excision, including lymphadenectomy for patients with proved carcinomatous changes.

Thomson¹⁵⁵ reports a case of *granulosis rubra nasi* in a ten-year-old boy. The patient had a symmetrically red sweating nose (involving the tip and midline to the bridge), and the normal and family history was negative for a similar defect. Williams believes the term "*granulosis*" should be deleted, with "*nevus*" as a substitute.

The report of schwannoma of the face, a rare skin tumor, is given by Thumin.¹⁵⁶ The twenty-one-year-old patient presented a tumor of four months' duration in the nasolabial-fold region. It was encapsulated, soft, friable, lobulated and gray, and measured approximately 4.0 by 1.5 by 1.0 cm. Microscopically, the tumor was diagnosed as *neurilemmoma*.

Blank¹⁵⁷ reports that in 88 patients with plantar warts he obtained 95 per cent cures with a new method of treatment. The wart is pared, and 90 per cent phenol is applied precisely to its surface, fuming nitric acid is then applied, causing a sputter. A round pad is applied, and finally 60 per cent salicylic acid. Walking is recommended to extrude the verruca, and five days later the lesion is observed and retreated if necessary. This is rather strenuous treatment, all three chemicals can cause great destruction of tissue.

Complications following the bismuth injection of verrucae is reported by Cameron.¹⁵⁸ A digital wart was injected with a drop of bismuth sodium tartrate. Two days later there was painful swelling of the area, with fever and axillary tenderness on palpation, but no lymphangitis. Cameron considers the case a toxic reaction to the heavy metal and believes that the risk does not justify such treatment of an innocuous wart. The same reaction can occur from an infection.

Kile and Welsh¹⁵⁹ have attempted to revive liquid oxygen in dermatologic practice, treating verruca vulgaris, condyloma acuminata, hemangioma, leukoplakia, seborrheic keratoses, senile keratoses, granuloma pyogenicum and folliculitis keloidalis. They report satisfactory response, with a soft scar that has not been followed by a keloid, even in persons prone to keloid. Its use in chronic discoid lupus erythematosus has been encouraging. Liquid oxygen was discarded many years ago in favor of better methods of therapy.

Sullivan and Blanchard,¹⁶⁰ after studying the reason for the action of podophyllotoxin on warts, conclude that it is the probable active ingredient of podophyllin.

McLellan¹⁶¹ describes the accidental discovery of a new method of treating senile warts. A patient who was suffering from fractured ribs was strapped with adhesive. On removal of the adhesive a few weeks later the senile warts were also removed.

Low-Beer¹⁶² used radioactive phosphorus in the treatment of basal-cell carcinomas, warts and hemangiomas and found the results very satisfactory. Radioactive phosphorus of the measured amount was placed on blotting paper and applied to the lesion. It produces a beta radiation.

Eberhard¹⁶³ reports the results of treatment of 492 cases of epitheliomas with a total of 760 lesions. Treatment consisted of surgery with a cold knife (no cautery or electric knife), fractionated x-ray therapy or interstitial radium. The choice of treatment depended on the size and location of the lesion, as well as the cosmetic effect, and not on histology. Biopsy is advocated to make sure the lesion belongs in the epithelioma group. A three-year follow-up study showed 66 per cent of patients living and free of epithelioma, 18 per cent had died of other diseases. By statistical analysis the cure rate was 83.3 per cent, which according to Eberhard compares favorably with general results obtained by others. There was no statistically significant difference in the results obtained by the three methods of treatment. Discussing the paper, Ullmann claimed considerably higher cure rates.

The feature of chemosurgical treatment of facial cancer, according to Mohs,¹⁶⁴ is microscopical control, using zinc chloride fixative paste after keratin is made penetrable by dichloroacetic acid. Surgery is determined by the microscopical examination of the zinc chloride fixed tissue. Two hundred and thirty-two basal-cell and 103 squamous-cell cancers were treated, with 100 per cent and 84 per cent cures respectively. I fail to see any improvement over complete surgical excision, except when a cosmetic result is not important. Pictures of their results were excellent.

Considering the action of podophyllum on normal skin, condylomata acuminata and verrucae vulgares, Sullivan and King¹⁶⁵ believe the substance is a potent cutaneous sensitizer. They report that the alcoholic solution is more advantageous than the oily suspension. The effect is on epithelial cells, consisting of degenerative action and production of bizarre cell forms interpreted as distorted mitotic figures (similar to colchicine figures). Podophyllo-toxin is probably the substance in the resin of podophyllum responsible for the cytotoxic effect, since the resin in sodium and potassium hydroxide had no effect on condylomata acuminata. I prefer the alcoholic solution. The patient should be warned regarding the subsequent discomfort for three or four days.

CONCLUSION

This review emphasizes the interest in cutaneous medicine evidenced by physicians who are not dermatologists. The majority of these observations were taken from journals not devoted to dermatology.

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Examination of the urine was negative. Examination of the blood disclosed a red-cell count of 3,600,000, with a hemoglobin of 8.5 gm, and a white-cell count of 8800, with 79 per cent neutrophils. There was moderate constant achromia and variation in size, with slightly smaller than normal red blood cells. The total protein was 6.1 gm per 100 cc, the sodium 130.9 and the chloride 96 milliequiv per liter, and the prothrombin time 21 seconds (normal, 16 seconds). The stools were light colored and guaiac negative.

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One thinks for a moment in passing of the history of weight loss, gastrointestinal distress and marked weakness and fatigue, which are mentioned, in the presence of a blood sodium of 130 milliequivalents per liter, and one wonders about adrenal hypofunction. However, lacking any mention of abnormality in the blood pressure or pigmentation or axillary-hair distribution and with positive mention that the menstrual history was normal, I am inclined to think that any disorder of adrenal function was secondary to the cachectic state rather



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to do what I thought was the most radical operation for cancer of the stomach on the basis that we might be dealing with that disease. A total gastrectomy was done, and it looked as if the stomach grossly were completely involved except possibly the part just proximal to the pylorus.

Another interesting clinical observation is that almost immediately after operation the temperature came down to normal. It was not as high the next day as it had been the day before operation. Then she ran for ten days a perfectly flat normal chart. After that she began to run another wave of fever, which was coincident with the usual dose of x-ray treatment, which she has been having and has just completed. Then we gave penicillin empirically, and after a period of ten days the temperature came down, and she then ran another normal temperature for a period followed by another short episode of fever. And now, once again, the temperature is down. Whether that has any significance as far as the primary disease goes, I do not know. It had no correlation with any obvious complication — no abscess, empyema, pulmonary infection or anything that we could find.

At one time there was a small accumulation of air and fluid beneath the left leaf of the diaphragm, but after a period of time it disappeared. The patient is going home tomorrow.

DR ADAMS: Did the blood picture improve?

DR SWEET: She continued to look more and more miserable as x-ray treatment progressed. After what was interpreted as a normal hemoglobin level before, during and after operation, the hemoglobin fell to 6 gm during the course of the treatment. She is having more transfusions in anticipation of discharge. She was very much nauseated by the x-ray therapy. We have hopes that she will improve now that we have stopped x-ray treatment.

Incidentally, we took out the spleen and terminal half of the pancreas, not because they were involved but because it was technically the only way I could get all the lymph nodes around the celiac axis.

DR MALLORY: We found that the stomach was entirely involved with tumor. There seemed to be two centers of tumor from which the lesion spread to involve virtually all the mucosa. One of these was shallowly ulcerated. A number of lymph nodes were obviously replaced by tumor, whereas others were normal. The histologic picture showed a very undifferentiated tumor, with a great many multinucleated cells in it, and our diagnosis was lymphoma of the Hodgkin's-sarcoma type. Some of the lesions in the lymph nodes were more characteristic of Hodgkin's disease than the stomach itself. The spleen was entirely uninvolved.

DR BENEDICT: I think this case represents one of the most important potential uses for the new gastroscope — namely, the differential diagnosis between gastritis, lymphoma and diffuse carcinoma

of the stomach. We have done 31 cases, of which 18 had chronic gastritis and 2 acute and chronic gastritis, and 8 showed normal stomachs, 1 lymphoma and 1 carcinoma.

DR MALLORY: Very frequently in lymphoma of the stomach the lesion is diffuse and grossly shows mucosal folds that, by x-ray examination, are indistinguishable from the hypertrophic type of gastritis.

DR SWEET: One of our medical staff who saw the patient raised the question of obtaining a bone-marrow biopsy. I wonder if we had done it whether it would have assisted us in making the diagnosis.

DR ADAMS: Before the routine studies were completed, we thought that a bone-marrow biopsy might be necessary to exclude leukemia. It would have been done had the other findings not crystallized the situation for us. I do not believe that it would have helped establish a diagnosis of lymphoma unless, in doing the biopsy, one was fortunate enough to stick the needle into a lymphomatous lesion in the bone marrow.

If Dr Benedict is including this case in a statistical study, he should not, in my opinion, include it as a case clinically diagnosed as gastritis. Before operation we were quite certain that we were dealing with a malignant lesion, probably lymphoma. The clinical diagnosis of gastritis was not considered.

If Dr Benedict is thinking in terms of statistics, I do not believe he should include this as a case of clinical gastritis in which lymphoma was discovered because we were quite certain we were dealing with a malignant lesion.

DR SWEET: Yes, and in the stomach.

DR WYMAN: The only point I want to make about x-ray treatment and anemia is that from our point of view it seems probable that she had extensive bone-marrow disease, which was accounting for the anemia, and this was not produced by x-ray treatment.

DR SWEET: Perhaps I gave the wrong impression. I did not mean to imply that there was a causal relation, it was merely an observation.

CASE 35092

PRESENTATION OF CASE

A seventy-nine-year-old retired mechanic entered the hospital because of vomiting, weakness and weight loss.

The patient was first seen in the Out-Patient Department seven years before, when he complained of intermittent attacks of epigastric burning and fullness of three or four years' duration. The discomfort was relieved by food and alkalis. There was some weight loss, but no nausea, vomiting or melena. Physical examination at that time revealed tenderness with some resistance in the epigastrium. An x-ray examination revealed the

patient to have had so many symptoms directly related to the gastrointestinal tract

One might consider liver disease, but I think liver disease presenting such marked fever and so much interference with gastrointestinal function and weight loss would have other earmarks that would point to the liver—either enlargement, telangiectasis, positive laboratory findings or jaundice. I am inclined to think this was not primarily liver disease.

The condition that in my mind answers the cachexia, the x-ray findings and the febrile course of the disease is one of the lymphoma or Hodgkin's group, and I would imagine that of these lymphoma is more apt to involve the stomach. I think these findings in the stomach were perfectly consistent with that diagnosis, and I would guess that, in addition to the involvement of the stomach, since there had been so much fever, the surgeon found involvement of the mesenteric and possibly retroperitoneal lymph nodes. I believe it is the experience of the X-ray Department that in lymphoma, when there is fever with no obvious explanation, the seat of the trouble is apt to be in these obscurely hidden lymph nodes. I am going to commit myself to a diagnosis of one of the lymphoma group, involving the stomach and probably the mesenteric and retroperitoneal lymph nodes.

DR TRACY B MALLORY: Would you like to add anything, Dr Adams?

DR F DENNETTE ADAMS: No, but I might say that my final reasoning was similar to Dr Graham's.

DR WYMAN: From the x-ray point of view, without the available clinical and laboratory data, one would have to consider hypertrophic gastritis also because of the enlarged gastric rugae.

DR ALLEN G BRAILEY: The fever was slightly high, was it not, to be explained on the basis of lymphoblastoma?

DR GRAHAM: I think it was consistent with that diagnosis. The thing that bothered me about it was that it was described as a spiking temperature, whereas the Pel-Ebstein type is less apt to be up and down. I am sure it is possible because I have seen it as high as this and even higher.

DR EDWARD B BENEDICT: We did a gastroscopy on this patient. There was no normal mucosa visible in any part of the stomach. The gastric wall presented a nodular appearance throughout. The angulus was distorted and somewhat rigid, and the gastric wall did not respond normally to air inflation. In other words, there was some evidence of rigidity. My first bet from the gross appearance was lymphoma, and I was fortunate that with the new operating gastroscope it was possible to get a satisfactory biopsy.

CLINICAL DIAGNOSIS

Lymphoma of stomach?

DR GRAHAM'S DIAGNOSIS

Lymphoma of stomach and mesenteric and retroperitoneal lymph nodes

ANATOMICAL DIAGNOSIS

Malignant lymphoma, Hodgkin's-sarcoma type, of stomach

PATHOLOGICAL DISCUSSION

DR MALLORY: Dr Benedict obtained a biopsy that clearly showed the presence of a malignant tumor. We were unable from the biopsy to make a certain diagnosis as to the type of neoplasm. We hesitated between carcinoma and lymphoma and eventually decided that it was a little more probable that it was carcinoma. Later we had reason to change our minds because Dr Sweet operated on the patient, and he will tell us the operative findings.

DR RICHARD H SWEET: May I say a word or two about the clinical appearance? This patient was sent to the hospital through my office. I did not see her before she arrived. She was referred to me by a physician who has always sent me thyroid cases and rarely anything else. At any rate, that is why the iodine entered the picture, because he had made a diagnosis of thyrotoxicosis and started her on iodine before she came to the hospital. We thought the elevation of the temperature might explain the increased basal metabolic rate. We found in the hospital that it was not as high as reported outside and immediately discarded that diagnosis.

I must confess that if we had not done a gastroscopy and not had the technical skill of Dr Benedict to obtain a biopsy through this new mysterious instrument of his, I would have made a definite diagnosis, purely on clinical grounds, of lymphoma of the stomach. When I heard that Dr Mallory, whose opinion I respect, was leaning toward carcinoma, I said "Well, I suppose it is carcinoma." When we saw the stomach at operation we could not tell grossly whether it was lymphoma or carcinoma. The only thing different was—this is from the clinical surgeon's point of view, not the pathologist's—the gross appearance of the lymph nodes was not like that in metastatic carcinoma. They were large, pink, juicy-looking things—more like inflammation or lymphoma. There was no evidence of lymph nodes in the mesentery, and nothing abnormal in the spleen or liver. We did the operation transthoracically or rather abdominotheracically and had an opportunity to investigate the left chest. There was nothing wrong there. But to extirpate as much of the disease as possible I took out the whole omentum and all the lymph nodes along both curvatures of the stomach, along the left gastric artery, and all the nodes around the abdominal segment of the esophagus. I endeavored

to do what I thought was the most radical operation for cancer of the stomach on the basis that we might be dealing with that disease. A total gastrectomy was done, and it looked as if the stomach grossly were completely involved except possibly the part just proximal to the pylorus.

Another interesting clinical observation is that almost immediately after operation the temperature came down to normal. It was not as high the next day as it had been the day before operation. Then she ran for ten days a perfectly flat normal chart. After that she began to run another wave of fever, which was coincident with the usual dose of x-ray treatment, which she has been having and has just completed. Then we gave penicillin empirically, and after a period of ten days the temperature came down, and she then ran another normal temperature for a period followed by another short episode of fever. And now, once again, the temperature is down. Whether that has any significance as far as the primary disease goes, I do not know. It had no correlation with any obvious complication—no abscess, empyema, pulmonary infection or anything that we could find.

At one time there was a small accumulation of air and fluid beneath the left leaf of the diaphragm, but after a period of time it disappeared. The patient is going home tomorrow.

DR ADAMS: Did the blood picture improve?

DR SWEET: She continued to look more and more miserable as x-ray treatment progressed. After what was interpreted as a normal hemoglobin level before, during and after operation, the hemoglobin fell to 6 gm during the course of the treatment. She is having more transfusions in anticipation of discharge. She was very much nauseated by the x-ray therapy. We have hopes that she will improve now that we have stopped x-ray treatment.

Incidentally, we took out the spleen and terminal half of the pancreas, not because they were involved but because it was technically the only way I could get all the lymph nodes around the celiac axis.

DR MALLORY: We found that the stomach was entirely involved with tumor. There seemed to be two centers of tumor from which the lesion spread to involve virtually all the mucosa. One of these was shallowly ulcerated. A number of lymph nodes were obviously replaced by tumor, whereas others were normal. The histologic picture showed a very undifferentiated tumor, with a great many multinucleated cells in it, and our diagnosis was lymphoma of the Hodgkin's-sarcoma type. Some of the lesions in the lymph nodes were more characteristic of Hodgkin's disease than the stomach itself. The spleen was entirely uninvolved.

DR BENEDICT: I think this case represents one of the most important potential uses for the new gastroscope—namely, the differential diagnosis between gastritis, lymphoma and diffuse carcinoma

of the stomach. We have done 31 cases, of which 18 had chronic gastritis and 2 acute and chronic gastritis, and 8 showed normal stomachs, 1 lymphoma and 1 carcinoma.

DR MALLORY: Very frequently in lymphoma of the stomach the lesion is diffuse and grossly shows mucosal folds that, by x-ray examination, are indistinguishable from the hypertrophic type of gastritis.

DR SWEET: One of our medical staff who saw the patient raised the question of obtaining a bone-marrow biopsy. I wonder if we had done it whether it would have assisted us in making the diagnosis.

DR ADAMS: Before the routine studies were completed, we thought that a bone-marrow biopsy might be necessary to exclude leukemia. It would have been done had the other findings not crystallized the situation for us. I do not believe that it would have helped establish a diagnosis of lymphoma unless, in doing the biopsy, one was fortunate enough to stick the needle into a lymphomatous lesion in the bone marrow.

If Dr Benedict is including this case in a statistical study, he should not, in my opinion, include it as a case clinically diagnosed as gastritis. Before operation we were quite certain that we were dealing with a malignant lesion, probably lymphoma. The clinical diagnosis of gastritis was not considered.

If Dr Benedict is thinking in terms of statistics, I do not believe he should include this as a case of clinical gastritis in which lymphoma was discovered because we were quite certain we were dealing with a malignant lesion.

DR SWEET: Yes, and in the stomach.

DR WYMAN: The only point I want to make about x-ray treatment and anemia is that from our point of view it seems probable that she had extensive bone-marrow disease, which was accounting for the anemia, and this was not produced by x-ray treatment.

DR SWEET: Perhaps I gave the wrong impression. I did not mean to imply that there was a causal relation, it was merely an observation.

CASE 35092

PRESENTATION OF CASE

A seventy-nine-year-old retired mechanic entered the hospital because of vomiting, weakness and weight loss.

The patient was first seen in the Out-Patient Department seven years before, when he complained of intermittent attacks of epigastric burning and fullness of three or four years' duration. The discomfort was relieved by food and alkalis. There was some weight loss, but no nausea, vomiting or melena. Physical examination at that time revealed tenderness with some resistance in the epigastrium. An x-ray examination revealed the

esophagus to be normal except for slight compression from a tortuous aorta just above the diaphragm. The fundus of the stomach appeared to be deformed, probably owing to extrinsic pressure. The pylorus opened readily, outlining a markedly deformed duodenal cap, with several large pouches on each curvature. In the narrowest portion of the cap there was a 1-cm crater, probably on the posterior wall. Diet and antacids gave relief, but approximately a year later he became weak, vomited black liquid and passed a black stool. He was anemic, with a hemoglobin of 8.1 gm, but he preferred not to be hospitalized. Several weeks later an x-ray film showed a deformed duodenum with a tiny ulcer crater on the posterior wall. On rest, diet and antacids he improved but remained weak. Three years before admission epigastric discomfort recurred following dietary indiscretions. An x-ray film again showed a deformed duodenum with an active ulcer. Five months previous to admission weakness, weight loss and anorexia developed, and later he had a single episode of severe epigastric pain, which "doubled him up" and required an injection by his doctor. He became more anorexic, weaker and finally bedridden. There was no hematemesis or melena, but he vomited all food he ingested in the two weeks prior to admission. Five days before entry he began to hiccup and developed pain in the left shoulder.

Physical examination showed a wasted man hiccuping constantly. The breath was not uremic. The tongue was coated and dry. There was marked kyphosis. The heart was slightly enlarged. The liver edge was percussible two fingerbreadths below the costal margin. There was tenderness in the left upper quadrant, and a hard, irregular edge could be felt under the left rib margin.

The temperature was 99.6°F, and the pulse 68. The blood pressure was 110 systolic, 70 diastolic.

The urine gave a ++ test for albumin, and the sediment contained many granular casts, occasional white blood cells and rare red blood cells. The hemoglobin was 11.5 gm. The white-cell count was 17,200, with 87 per cent neutrophils. The serum protein was 6.3 gm per 100 cc. The chloride was 97 milliequiv per liter, and the nonprotein nitrogen 5.4 mg and the fasting blood sugar 136 mg per 100 cc. The prothrombin time was 18 seconds (normal, 15 seconds). A gastrointestinal series was reported as follows:

The esophagus is quite normal as to form and function, except for the fact that it retains barium longer than usual, apparently owing to pressure upon its lower end by some thing beneath the diaphragm, which also is consistent with pressure and deformity of the fundus of the stomach. The fundus and body of the stomach are displaced anteriorly. There is an irregular pooling of barium in the fundus just below the cardia. Within the hollow of the displaced stomach there are several areas of translucency that look like air, a few other areas look like barium. These dense flecks are seen on the film made several years ago. The duodenal bulb is constantly deformed in the manner characteristic of ulcer. An ulcer crater 0.5 cm in size is present.

A chest film showed scoliosis of the spine and mild arthritic changes.

During the hospital stay the temperature spiked daily to 101 and 102°F, with an average pulse rate of about 105. Examination of the blood on the fourth day showed a white-cell count of 33,200, with "marked neutrophilia and toxic granules." Attempts to pass a tube from the esophagus into the stomach were unsuccessful. On the sixth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR HORATIO ROGERS: I think we can assume that eleven years before admission this man had ulcer symptoms, seven years before admission he still had ulcer symptoms, and x-ray films demonstrated duodenal ulcer. One year later he had a gastrointestinal hemorrhage, presumably from the duodenal ulcer, three years before admission he still had ulcer symptoms, and x-ray examination demonstrated an active duodenal ulcer. All this past history would be consistent with a simple duodenal ulcer if it were not for that one x-ray note about the fundus of the stomach being deformed by extrinsic pressure seven years before admission.

It seems that the present illness began five months before entry. Within five months there was progressive weight loss, weakness and anorexia. The patient was seventy-nine years old, so that one immediately thinks of cancer, possibly in the stomach. Then he had an episode of severe epigastric pain, doubling him up and requiring an injection. We do not know just how long before admission that was, but presumably very recently. That makes me wonder about perforation of the old ulcer or possibly hemorrhage into a cyst. It may have been a cyst behind the stomach, that would go with the x-ray description of extrinsic deformity of the

stomach Hemorrhage into a pancreatic cyst could cause a severe, acute episode of epigastric pain, such as this man had. Then he developed vomiting, and he vomited everything. Whether that was really vomiting or regurgitation may be important, because if his stomach was obstructed at the cardia, it could not have been vomiting, it must have been regurgitation. Then he developed hiccuping and pain in the left shoulder, which suggests irritation of the left leaf of the diaphragm. So from the history alone we might assume that he had something in the lesser peritoneal cavity that formed the x-ray shadow that deformed the stomach and pushed it forward and was presumably associated with an acute episode of epigastric pain from which he rapidly went downhill.

I would like to see the x-ray films because there are a number of things I do not understand, particularly the note about flecks of barium seen in the examination years previously in the hollow of the displaced stomach. Does that mean in the stomach itself?

DR STANLEY M. WYMAN: There are only three films remaining from the x-ray examination of this patient, unfortunately. The first film was taken seven years before the last. The second film was taken four years after the first, and three before the last. The flecks of density described are seen at this point on the original examination lying apparently quite close to the stomach. There is definite compression of this portion of the cardia, with a suggestion of a soft-tissue density in the adjacent region. The deformity of the duodenal bulb is imperfectly visualized, but I believe it is present. The second film taken four years later shows the fleck of density to have been displaced more posteriorly. The films were taken in quite similar projection. I believe this is a true observation, particularly in view of the last film, which shows the density to have been pushed still farther posteriorly and downward. The second film shows a suggestion of a sharp angle in the upper part of the stomach and, again, a soft-tissue mass, which on the last film extends along the midbody down close to the angle, in a hemispherical fashion, and indenting the cardia. The small shadows of rarefaction seen here, I believe, lie in the soft-tissue mass and probably represent gas. The general configuration and contour of this lesion, with the sharp angle where the mass joins

normal stomach, are consistent with an adherent mass or an intramural mass.

DR ROGERS: Do we have to suppose that these flecks are barium, or can we think that they are calcium?

DR WYMAN: I think calcium is perhaps a better bet.

DR ROGERS: On physical examination the patient was emaciated and had a hemoglobin of 8.1 gm, which is less anemia than one would expect with cancer of the stomach of this extent. He had casts and albumin in the urine and nonprotein nitrogen of 54 mg per 100 cc., indicating kidney damage, but not enough to make me suspect the kidney as the primary source of his trouble. He had an elevated temperature and a rising white-cell count, which would make one think of either sepsis or necrosis. He had a prothrombin time only slightly elevated, and the liver edge could be palpated two fingerbreadths below the costal margin. It does not indicate anything very important associated with the liver to me. The blood sugar was 136 mg per 100 cc., and the top normal would be 100 mg, so that is a definite elevation and immediately makes one think of the carbohydrate metabolism and wonder about the function of the pancreas. We do not have any amylase or lipase or glucose tolerance report so probably that was not seriously considered on the wards.

Then we come to the hard, irregular, tender mass in the left upper quadrant. Apparently that is the thing we have to guess the nature of. Was it a malignant tumor in the stomach itself? I should think that the slightness of his anemia, his lack of bleeding and the seven-year duration of gastric deformity were all against it. It could be retroperitoneal malignant sarcoma of some form, but the present course seems to have been rapidly progressive, yet we have x-ray evidence of its presence seven years before admission. It could hardly have been a malignant tumor going on all that time. A possible explanation would be a mass that remained benign for several years and then more recently became malignant. We could explain the acute episode just before admission on the basis of either necrosis of a malignant tumor or hemorrhage into a malignant pancreatic cyst. I think that cancer of the body or tail of the pancreas would be my best bet. There are a number of things about cancer of the tail of the pancreas that are characteristic and ap-

esophagus to be normal except for slight compression from a tortuous aorta just above the diaphragm. The fundus of the stomach appeared to be deformed, probably owing to extrinsic pressure. The pylorus opened readily, outlining a markedly deformed duodenal cap, with several large pouches on each curvature. In the narrowest portion of the cap there was a 1-cm crater, probably on the posterior wall. Diet and antacids gave relief, but approximately a year later he became weak, vomited black liquid and passed a black stool. He was anemic, with a hemoglobin of 8.1 gm, but he preferred not to be hospitalized. Several weeks later an x-ray film showed a deformed duodenum with a tiny ulcer crater on the posterior wall. On rest, diet and antacids he improved but remained weak. Three years before admission epigastric discomfort recurred following dietary indiscretions. An x-ray film again showed a deformed duodenum with an active ulcer. Five months previous to admission weakness, weight loss and anorexia developed, and later he had a single episode of severe epigastric pain, which "doubled him up" and required an injection by his doctor. He became more anorexic, weaker and finally bedridden. There was no hematemesis or melena, but he vomited all food he ingested in the two weeks prior to admission. Five days before entry he began to hiccup and developed pain in the left shoulder.

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DOCTORS' PROGRAM

THE meeting of the Planning Committee of the American Medical Association was held, as scheduled, in Chicago on February 12. Composed of the officers of the Association and representatives of the Board of Trustees and the House of Delegates, the committee was augmented by the secretary and one other member of each state medical society and other interested persons. Its purpose was to present a plan of action for the American Medical Association to follow in bettering its relations with the public and in acquainting the public with the practices of American medicine, and to consider a constructive program for improving the distribution of medical care in this country.

These objectives are those for which many of the critics of the Association have been clamoring since the assessment was announced in December and for the preparation of which adequate time was necessary.

A revitalized public-relations plan is in the hands of the firm of Whitaker and Baxter, of San Francisco, which has opened offices for the purpose in Chicago. The plan is first to neutralize the smear attack on the subject of lobbying and a "slush fund" that has been launched against the Association, and next to organize an educational campaign that will reach the people of the United States through the individual members of the Association and all interested persons and organizations. This campaign will emphasize the desirability of free enterprise in medicine and the extension of voluntary prepayment plans, as opposed to the principle of compulsory health insurance.

These are the purposes for which the assessment levied by the Association is already being expended, every dollar of which will be reported in a check-by-check accounting to the Association, with financial reports available for Government inspection at any time.

In addition, a twelve-point program for the advancement of medicine and public health is proposed. These points, in brief, consist of

- 1 Creation of a federal Department of Health of Cabinet status with a secretary who is a Doctor of Medicine, and the co-ordination and integration of all federal health activities under it, except for those of the medical services of the armed forces.
- 2 Promotion of medical research through a National Science Foundation, with grants to private institutions.
- 3 Further development and wider coverage by voluntary hospital and medical care plans to meet the costs of illness, with aid through the states to the indigent and medically indigent.
- 4 Establishment in each state of a medical care authority to receive and administer funds with proper representation of medical and consumer interest.

pear in this case. For instance, the surprisingly high hemoglobin for such a sick man, the hyperglycemia, the extreme weight loss and the rapid downhill course at the end. He did not have jaundice, the other common sign of pancreatic cancer, because the mass was not near the common duct.

DR J H MEANS Could this have been a leiomyoma of the stomach? My recollection is that they may exist in benign fashion for a number of years and take on rapid malignant growth terminally. The roentgenologist said it seemed as if it were in the wall of the stomach, which is where leiomyoma would develop. It could have perforated, I suppose, as a terminal event.

DR WYMAN I think that is an excellent suggestion and should be considered most seriously. Perhaps I did not emphasize sufficiently the pockets of probable gas lying in the mass. They have to be explained by gas-forming organisms or, more logically, by the entrance of gas into the mass from a gas-containing viscus.

DR TRACY B MALLORY Dr FitzHugh, would you like to comment?

DR GREENE FITZHUGH I thought that the tumor did not originate in the stomach and believed as Dr Rogers did that the best possibility was the pancreas.

DR PERRY J CULVER Would deposits of fat reduce x-ray opacity enough to cause such spots of radiolucency?

DR WYMAN Fat deposits have the same x-ray density as air, but they are not present on the original two films and, therefore, one must assume that they have developed since then.

DR CULVER I was thinking of fat necrosis with pancreatic tumor.

DR WYMAN I do not believe it would produce this appearance.

DR MALLORY Fat necrosis would probably cause a dense shadow because it tends to calcify very fast.

CLINICAL DIAGNOSIS

Perforated malignant tumor, with abscess formation

DR ROGERS'S DIAGNOSES

Malignant degeneration of pancreatic cyst
Duodenal ulcer, old

ANATOMICAL DIAGNOSES

Neurofibrosarcoma of stomach, with metastases to liver and perforation into abdominal cavity

Peritonitis, acute, generalized, mild
Arteriosclerosis, generalized, moderate
Emphysema, pulmonary

PATHOLOGICAL DISCUSSION

DR MALLORY This patient was explored in the very forlorn hope that there might be a localized abscess that could be drained. At operation Dr Parsons found a large tumor mass arising from the lesser curvature of the stomach, firmly attached to it. He was unable to do anything but take a biopsy. There was slight peritonitis present, but the patient died within twenty-four hours.

At autopsy a large tumor was found occupying about half the lesser curvature, lying almost entirely intramurally. Its center was eroded, and perforation had resulted. It was a spindle-cell sarcoma — we thought more likely fibrosarcoma than leiomyosarcoma. That differentiation is often a difficult one to make. There was one single large metastasis to the liver — a round spherical nodule, nearly 6 cm in diameter. No other metastases were found. We were able to find the scar of his old duodenal ulcer, which seemed entirely healed. The other findings were only those consistent with his age, such as generalized arteriosclerosis and pulmonary emphysema, neither of them severe.

It is possible that Government may so reform its methods as to make a vast federal insurance scheme run smoothly, efficiently and economically, but it is the policyholders who would be taking the uncalculated risk — under compulsion

Certain conclusions are obvious. Momentous decisions are in the making, and the order changeth, in one way or another. It must be accepted that all honest advocates either of Government control and compulsory insurance or of free enterprise and voluntary insurance have the same interest at heart — the best possible medical care for all the people who can be reached. Each faction, if factions there must be, may make one of its greatest contributions to the attainment of this common goal by trying to understand and appraise the opinions of the other.

There can be no disagreement with Dr Butler's closing sentence in which, referring to the Suffolk District and the Massachusetts Medical societies, he writes "the past history of both societies amply justifies the expectation that considered thought will result in much needed tolerant discussion, intelligent decisions and constructive action."

NITROGEN CYCLE

THE world is full of headaches these days, and one of the major ones that will remain after a *modus vivendi* has been achieved between Russia and the rest of the world, the Jews and Arabs have been appeased in Palestine and some sort of low-cost medical care has been provided for our own people is the truly frightening contemporary fulfillment of the dire prophecies made exactly one hundred and fifty years ago by Thomas R. Malthus in his "Essay on Population as it Affects the Future Improvement of Society." The world is running out of food.

Hopefully the UN presents a possible solution. Among that body's multifarious assortment of organizations to plan for a brave new future are the WHO, or World Health Organization, and the FAO, or Food and Agricultural Organization. Experts in the two organizations are convinced that a world problem of such vast and complicated nature as the present universal food shortage cannot possibly

be solved by any short-term emergency schemes. Something more effective and more enduring than mere relief projects must be undertaken. WHO and FAO propose action for more food through better health.* It seems that an important reason why the world's farmers cannot produce enough food is that they are not enjoying the good health usually attributed to tillers of the soil.

At least ten million acres of potentially rich agricultural land are now being worked by disease-ridden people. The two organizations estimate that the enduring and effective project they have in mind could be carried out over this area at a cost of only twenty cents per acre per year. During a trial period of five years this would require the expenditure of only ten million dollars.

What can be done for these ten million acres at twenty cents each? The answer is simply to spray them with DDT. Malaria, the greatest scourge, might by this simple expedient be wiped out entirely or at least controlled beyond the point of being a real danger any longer. Thus, the low agricultural output would be increased per man and per acre, contributing directly to the alleviation of the world food scarcity and creating almost immediately a spirit of enterprise and self-respect among men who had previously believed that they were the slaves of their environment and not its masters.

WHO and FAO suggest that introduction of proper methods in the combined use of agricultural machinery, adequate draft power, correct fertilizers, and so forth is also desirable, and perhaps might be accomplished to some extent at the same rate of twenty cents per acre. The plan seems at least worth trying.

NATIONAL GUARD NEEDS MEDICAL PERSONNEL

ATTENTION is directed to the communication from Colonel Chamberlin published elsewhere in this issue of the *Journal*. Eligible members of the profession, somewhat blinded by the publicity that is shed on the medical-personnel requirements of the country's expanding military and naval establishments, may fail to realize the opportunities that the National Guard has to offer.

**WHO Newsletter*, Vol. 2, No. 10, October 1948. New York: Public Information Office, World Health Organization.

5 Encouragement of prompt development of diagnostic facilities, health centers and hospital services, locally originated for areas in which the need can be shown

6 Establishment and improvement of local public-health units and services, with remuneration of health officials commensurate with their responsibility

7 The development of a program of mental hygiene with aid to mental-hygiene clinics in suitable areas

8 Health education programs administered through suitable state and local health and medical agencies

9 Provision of facilities for care and rehabilitation of the aged and those with chronic disease and various other groups not covered by existing proposals

10 Integration of veterans' medical care and hospital facilities with other medical care and hospital programs

11 Greater emphasis on the program of industrial medicine, with increased safeguards against industrial hazards and prevention of accidents occurring on the highway, in the home and on the farm

12 Adequate support, with funds free from political control, of the medical, dental and nursing schools and other institutions necessary for the training of specialized personnel required in the provision and distribution of medical care

Obviously any such program or parts of it to become effective will require legislation, which will presumably be proposed at the proper time

PUBLIC FINANCING IN MEDICINE

THE discourse on public financing of medical education, research, health and medical care, delivered last May by Dr Allan M Butler before the Suffolk District Medical Society and published elsewhere in this issue of the *Journal*, presents astutely and temperately certain arguments in favor of compulsory health insurance

It so happens, nevertheless, that the majority of the medical profession is at present opposed, and

it believes with reason, to this method of payment for medical services. What its attitude may be five, fifteen or fifty years hence is another matter, since it is the present that is under consideration. It is freely admitted, however, that principles having to do with the distribution of medical care that are accepted today were anathema ten or fifteen years ago.

The fact that in 1946 the Government spent \$1,200,000,000 for health and medical care is taken by Dr Butler as "a measure of the failure of philanthropy and private charity to meet the needs." Presumably the expenditures of the Veterans Administration are included in this figure, but aside from this no estimate is available as to how much of the colossal outlay was necessary, or how wisely and economically it was made. If this vast sum was expended with caution and judgment, and with due regard to conservation of the country's resources, then the employment of some part of it is certainly acceptable so far as present concepts are concerned. This applies especially to those allocations having to do with public health, with the care of communicable disease and mental illness, and to a considerable degree with research. There is, however, a line, indistinct as it may be, beyond which governmental encroachment may be justly considered as dangerous in that it may jeopardize the quality of medical care. There is still occasion, in our imperfect society, for skepticism regarding the efficiency of Government methods.

Published sections of the Hoover investigation give substance to this skepticism, as where it reports, in relation to the construction of Veterans Administration Hospitals, "The federal Government is assuming uncalculated obligations without any understanding of their ultimate cost, the lack of necessary professional manpower to carry them out, or their adverse effect upon the hospital system of the country." And again, "[there is a] pattern of duplication of physical facilities, waste of scarce medical personnel, and unwarranted construction of new facilities—all resulting primarily from the lack of a central plan for federal medical care."

It is possible that Government may so reform its methods as to make a vast federal insurance scheme run smoothly, efficiently and economically, but it is the policyholders who would be taking the uncalculated risk — under compulsion

Certain conclusions are obvious. Momentous decisions are in the making, and the order changeth, in one way or another. It must be accepted that all honest advocates either of Government control and compulsory insurance or of free enterprise and voluntary insurance have the same interest at heart — the best possible medical care for all the people who can be reached. Each faction, if factions there must be, may make one of its greatest contributions to the attainment of this common goal by trying to understand and appraise the opinions of the other.

There can be no disagreement with Dr. Butler's closing sentence in which, referring to the Suffolk District and the Massachusetts Medical societies, he writes "the past history of both societies amply justifies the expectation that considered thought will result in much needed tolerant discussion, intelligent decisions and constructive action."

NITROGEN CYCLE

THE world is full of headaches these days, and one of the major ones that will remain after a *modus vivendi* has been achieved between Russia and the rest of the world, the Jews and Arabs have been appeased in Palestine and some sort of low-cost medical care has been provided for our own people is the truly frightening contemporary fulfillment of the dire prophecies made exactly one hundred and fifty years ago by Thomas R. Malthus in his "Essay on Population as it Affects the Future Improvement of Society." The world is running out of food.

Hopefully the UN presents a possible solution. Among that body's multifarious assortment of organizations to plan for a brave new future are the WHO, or World Health Organization, and the FAO, or Food and Agricultural Organization. Experts in the two organizations are convinced that a world problem of such vast and complicated nature as the present universal food shortage cannot possibly

be solved by any short-term emergency schemes. Something more effective and more enduring than mere relief projects must be undertaken. WHO and FAO propose action for more food through better health.* It seems that an important reason why the world's farmers cannot produce enough food is that they are not enjoying the good health usually attributed to tillers of the soil.

At least ten million acres of potentially rich agricultural land are now being worked by disease-ridden people. The two organizations estimate that the enduring and effective project they have in mind could be carried out over this area at a cost of only twenty cents per acre per year. During a trial period of five years this would require the expenditure of only ten million dollars.

What can be done for these ten million acres at twenty cents each? The answer is simply to spray them with DDT. Malaria, the greatest scourge, might by this simple expedient be wiped out entirely or at least controlled beyond the point of being a real danger any longer. Thus, the low agricultural output would be increased per man and per acre, contributing directly to the alleviation of the world food scarcity and creating almost immediately a spirit of enterprise and self-respect among men who had previously believed that they were the slaves of their environment and not its masters.

WHO and FAO suggest that introduction of proper methods in the combined use of agricultural machinery, adequate draft power, correct fertilizers, and so forth is also desirable, and perhaps might be accomplished to some extent at the same rate of twenty cents per acre. The plan seems at least worth trying.

NATIONAL GUARD NEEDS MEDICAL PERSONNEL

ATTENTION is directed to the communication from Colonel Chamberlin published elsewhere in this issue of the *Journal*. Eligible members of the profession, somewhat blinded by the publicity that is shed on the medical-personnel requirements of the country's expanding military and naval establishments, may fail to realize the opportunities that the National Guard has to offer.

**WHO Newsletter*, Vol. 2, No. 10, October 1948. New York: Public Information Office, World Health Organization.

Enrolled in this permanent organization, trained to serve in the event of civil disaster as well as in that of wartime emergency, the medical officer has an unusual opportunity for discharging his military obligations in his own chosen outfit. Colonel Chamberlin's letter outlines the details of service and of pay for both physicians and medical students, as well as the important point of retirement income.

LITHIUM CHLORIDE

A small number of patients on low sodium diets who are receiving a salt substitute — Westsal — (Wess-sal) have been reported to have had toxic symptoms, especially muscle tremors, weakness, inco-ordination and gastrointestinal disturbances, possibly due to lithium. Any information concerning the occurrence of very rare fatalities is highly inconclusive.

The manufacturers are investigating the situation. Any physician who can report on the successful use of the preparation or its toxic effects should communicate with Howard B. Sprague, M.D., 1180 Beacon Street, Brookline, Massachusetts (telephone ASpinwall 7-1550), representing the New England Heart Association.

Fourth-year students in approved medical schools are reminded of the *Journal's* prize-essay competition on preventive medicine.

For further information see *The New England Journal of Medicine*, September 30, 1948, p. 525, or write to the editor.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

GALLAGHER — John V. Gallagher, of Milford, died on September 17. He was in his seventy-second year.

Dr. Gallagher received his degree from Tufts College Medical School in 1902. He was medical examiner of the Sixth Worcester District and was a member of the staff of Milford Hospital.

His widow, a daughter and a son survive.

SHERBURNE — Andrew E. Sherburne, M.D., of Portsmouth, New Hampshire, died on January 29. He was in his seventy-sixth year.

Dr. Sherburne received his degree from Harvard Medical School in 1903.

His widow, two sons and five grandchildren survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JANUARY, 1949

RÉSUMÉ

DISEASE	JANUARY 1949	JANUARY 1948	SEVEN YEAR MEDIAN
Chancroid	10	2	2*
Chicken pox	4155	2322	2274
Diphtheria	35	15	15
Dog bite	620	569	503
Dysentery bacillary	1	14	10
German measles	142	70	150
Gonorrhea	266	196	160
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	3	1	1*
Malaria	0	1	8
Measles	6024	1167	1167
Meningitis meningococcal	6	8	18
Meningitis Pfeiffer-bacillus	5	3	3
Meningitis pneumococcal	3	4	5
Meningitis staphylococcal	0	0	0
Meningitis streptococcal	0	0	0
Meningitis undetermined	5	2	6
Mumps	1633	1517	1113
Polio-myelitis	0	0	4
Salmonellosis	3	4	1200
Scarlet fever	1014	415	397
Syphilis	194	212	213
Tuberculosis, pulmonary	205	198	15
Tuberculosis other forms	12	8	2
Typhoid fever	0	2	2
Undulant fever	3	2	2
Whooping cough	304	454	612

*Five-year median

COMMENT

Diseases with incidence higher than the seven-year median were chicken pox, diphtheria, German measles, measles, mumps and undulant fever.

Diseases with incidence lower than the seven-year median were scarlet fever and whooping cough.

Chicken pox was highest for any January since reporting began.

Measles had a higher incidence twice before — in 1926 and 1934 — than for this January.

Scarlet fever is steadily increasing in prevalence and will probably be exceeding the median within the next few months.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Arlington, 1, Boston, 24, East Brookfield, 1, Lynn, 2, Medford, 3, Revere, 1, Somerville, 1, Watertown, 1, Winchester, 1, total, 35.

Dysentery, bacillary, was reported from Worcester, 1, total, 1.

Encephalitis, infectious, was reported from Brimfield, 1, Lunenburg, 1, Springfield, 1, total, 3.

Lymphocytic choriomeningitis was reported from Fall River, 1, Fitchburg, 1, total, 2.

Meningitis, meningococcal, was reported from Boston, 1, New Bedford, 1, Rowley, 1, Salem, 1, Wakefield, 1, Westfield, 1, total, 6.

Meningitis, Pfeiffer-bacillus, was reported from Lawrence, 1, New Bedford, 1, Springfield, 1, West Brookfield, 1, Westfield, 1, total, 5.

Meningitis, pneumococcal, was reported from Haverhill, 1, Tewksbury, 1, Weymouth, 1, total, 3.

Meningitis, undetermined, was reported from Adams, 1, Bedford, 1, Haverhill, 1, North Adams, 1, Pembroke, 1, total, 5.

Salmonellosis was reported from Boston, 2, New Bedford, 1, total, 3.

Septic sore throat was reported from Boston, 5, total, 5.

Tetanus was reported from Deerfield, 1, total, 1.

Trichinosis was reported from Fall River, 1, Mansfield, 1, Northampton, 1, Weymouth, 1, total, 4.

Tularemia was reported from Tisbury, 1, total, 1.

Undulant fever was reported from Marblehead, 1, Rutland, 1, Westboro, 1, total, 3.

MISCELLANY

VFW CRAVE CHIROPRACTIC

Bill 1512, introduced into the House of Representatives by Representative Walter B. Huber, Democrat, of Ohio, authorizes the appointment of chiropractors in the medical department of Veterans Administration, according to Washington Report on the Medical Sciences. The measure, similar to one sponsored last year by Representative Patterson of Connecticut, was filed at the request of Veterans of Foreign Wars.

Are not the veterans sticking their necks out in asking Government to pay to have them broken for them?

CORRESPONDENCE

OPPORTUNITIES IN THE NATIONAL GUARD

To the Editor I wish to take this opportunity of presenting to the physicians in the Greater Boston area, especially house officers and younger veterans of World War II, the desirability of joining the Massachusetts National Guard and more particularly the 114th Medical Battalion of the 26th Division, which I have the privilege of commanding. This organization is charged with second-echelon evacuation, triage, emergency surgery and early psychiatric therapy in combat. In peace we are training to accomplish these missions and in addition to be prepared to be of service in event of major civil disaster. Working in co-operation with civilian agencies, we as an organization are prepared to co-ordinate ambulance runs and to serve as an office of record for casualties, we have the facilities to set up quickly and efficiently a collecting station for treating, sorting and clearing casualties. Thus, a medical officer in this organization has the dual opportunity of preparing himself to serve usefully in time of war and to be of service to his community in the event of disaster.

There are other advantages of a more immediate character — namely, good fellowship in a slightly different atmosphere than usually exists in a physician's daily life, pay for two hours' work a week, and full pay and allowances for two weeks on Cape Cod in the summer. Since the passage of a civilian component retirement act by Congress last summer, service in the National Guard is the quickest and easiest way to earn the required points for a retiree's income at age sixty. Where else in the world can one set up an annuity and get paid for doing it?

Since the war, the 26th Division has been almost entirely reorganized. In the Medical Battalion all administrative duties are carried out by nonmedical personnel, so that no physician is required to take property responsibility, or worry about rosters, payrolls and the like. This is a much happier situation than many of the junior medical officers of the last war had. It assures a physician that he will be doing professional work only. I have vacancies for majors, captains and lieutenants — medical corps. Any physician who gained the rank of major, or its Navy equivalent, during the war or on a terminal leave promotion is eligible for the same rank in the 114th Medical Battalion. Any house officer or recent graduate without previous military service may obtain a commission as first lieutenant. A physician's status in any other civilian component of the armed services is not jeopardized, since, though it is necessary to vacate a reserve commission to accept one in the National Guard, a physician may resign at any time and revert to his previous status without prejudice or loss of seniority.

Medical students may also be of use to us in the ranks and may augment their incomes with the pay of the grade for which they qualify. There are numerous noncommissioned officer vacancies, which I will be happy to fill with qualified medical students. By enlisting in the 114th Medical Battalion, a medical student may not only earn a few extra dollars a week but also become familiar with the work of the Army Medical Department and become eligible immediately upon graduation for a commission as first lieutenant Medical Corps. The work is interesting, useful and not too arduous or time consuming and pays. We drill on Thursday nights at the South Armory, Irvington Street, Boston. I may be reached by telephone during the week at Commonwealth 6-5142.

DONALD T. CHAMBERLIN, COLONEL MC
Massachusetts National Guard

Boston

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

What Is Psychoanalysis? By Ernest Jones, M.D. 8°, cloth, 126 pp. New York: International Universities Press, 1948. \$2.00.

Dr. Jones, a recognized English authority on psychoanalysis, first drafted this small book in 1928. The author states that in this second edition he finds little that needs changing. In a short addendum he discusses briefly the modern trends and problems of psychoanalysis.

Correlative Neuroanatomy By Joseph J. McDonald, M.S., M.Sc.D., M.D., Joseph G. Chusid, A.B., M.D., and Jack Dange, M.S., M.D. 8°, cloth, 156 pp., with 60 illustrations. Fourth edition. Palo Alto, California: University Medical Publishers, 1948. \$3.00.

This students' manual was first published in 1938. It covers gross anatomy, neuroanatomy, neurodiagnosis and neurology and correlates anatomy and physiology with the clinical findings of diseases of the nervous system. The text is divided into three parts: the peripheral nerves, neurodiagnosis, and diseases of the central nervous system. An appendix gives a complete list of neurologic signs and symptoms, a brief discussion of muscular dystrophies and atrophies and an outline of the neurologic examination. A good index concludes the volume. The printing is done by a reproductive process. The outline illustrations are good and clear. The binding is of the ring type, common to students' notebooks.

Bright's Disease By Henry A. Christian, A.M., M.D., LL.D., Sc.D. (Hon.), M.A.C.P., Hon. F.R.C.P. (Can.), D.S.M. (Am. Med. Assoc.). Reprinted from *Oxford Loose-Leaf Medicine* with the same pagination. 8°, cloth, 384 pp., with 40 illustrations and 38 tables. New York: Oxford University Press, 1948. \$9.00.

This monograph brings the subject up to date and reflects the author's experience of forty-seven years in the study of kidney diseases, and presents his concept of the disease. The classification is the clinical one devised by Dr. Christian. A bibliography of 492 references concludes the text. There is a good index. The reprint of this important contribution makes it available to persons not having access to the loose-leaf system. The type, paper, printing and illustrations are excellent. The price is high but is probably justified by the complicated tables, charts and illustrations.

NOTICES

ANNOUNCEMENT

Dr. Henry H. Lerner announces the opening of his office for the practice of roentgenology at Physicians Hall, 314 Commonwealth Avenue, Boston.

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater of Building D, Harvard Medical School, on Tuesday, March 8, at 8 p.m. The chairman for the evening will be Dr. George W. Thorn.

PROGRAM

The Use of Fraction I for Separation of Erythrocytes and Leukocytes from Whole Blood. Edward S. Buckley, Jr., Marvin J. Powell and John G. Gibson, II.
The Role of the Hypothalamus in the Adrenal Cortical Response to Stress. David Hume, Peter H. Forsham and George Whittenstein.

Pulmonary Hypertension Lewis Dexter, Eugene Eppinger, James Whittenberger, Florence W Haynes, Harper K Hellems, James Dow, Benjamin Ferris and Walter Goodale

Effect of Sulfanilamide on Salt and Water Retention in Congestive Heart Failure William B Schwartz, Jr

The Measurement of the Exchangeable Potassium by Isotope Dilution Leslie Corsa, Richard Steenburg, Margaret Ball and Francis D Moore

Use of an Artificial Kidney John P Merrill, Edmund J Callahan, III, and George W Thorn

Subsequent meetings will be held on April 12 and May 10

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A meeting of the New England Society of Anesthesiologists will be held in the Auditorium of Building A, Boston University School of Medicine, 80 East Concord Street, Boston, on Tuesday, March 8, at 8 00 p m The scientific program will be as follows

Pain Problems in the Paraplegic Patient David P Crowell, M D

Technic and Anatomic Considerations of Stellate-Ganglion Block Edward J Twigg, M D

Reflex Sympathetic Dystrophy and Differential Spinal Block as a Diagnostic Aid Ruth M Anderson, M D

Physicians and medical students are invited

SOUTH END MEDICAL CLUB

The next luncheon meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, March 15, at 12 noon Dr Nathan Sidel will speak on the subject "Arthritis in General Practice"

Physicians are cordially invited to attend

AMERICAN ASSOCIATION OF INDUSTRIAL PHYSICIANS AND SURGEONS

The Industrial Physicians and Surgeons of the United States and Canada will hold their thirty-fourth annual meeting at Detroit, Michigan, April 2 to 9, with headquarters at the Book-Cadillac and Statler hotels Participating groups are the American Conference of Governmental Industrial Hygienists, the American Industrial Hygiene Association, the American Association of Industrial Dentists and the American Association of Industrial Nurses

EXAMINATIONS FOR APPOINTMENT IN NAVY MEDICAL CORPS

Examinations for the selection of candidates for appointment to the grade of lieutenant (junior grade) in the Medical Corps of the Navy will be conducted at all Navy hospitals in continental United States during the period April 4-8, 1949

Graduates of approved medical schools in the United States or Canada who have completed intern training in accredited hospitals or who will complete such training within four months of the date of the examination, and who are physically and otherwise qualified, may be examined for appointment as lieutenant (junior grade) in the Navy Medical Corps Candidates must be less than thirty-two years of age at the time of appointment

Candidates will be required to appear before boards of medical examiners and supervisory Navy examining boards at the Navy hospital nearest their place of residence to demonstrate their physical and professional qualifications for appointment Following approval by the President of the United States and confirmation by the Senate, selected candidates will be issued appointment and orders assigning them to duty in a Navy medical facility for active service

As a result of the authorized additional compensation of \$100 a month for medical officers, a lieutenant (junior grade) in the Navy Medical Corps receives pay and allowances totaling \$5,011 a year if married, and \$4,575 50 if without dependents

Detailed information concerning the form and procedure of application may be obtained from the nearest Navy Officer Procurement office or from the Bureau of Medicine and Surgery, Navy Department, Washington 25, D C (Attn Code-3424)

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY, INC

The general oral and pathology examination (Part II) for all candidates will be conducted at Chicago, Illinois, by the entire Board from Sunday, May 8, through Saturday, May 14, 1949 The Hotel Shoreland in Chicago will be the headquarters for the Board Formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates Hotel reservations may be made by writing direct to the Shoreland

Candidates for re-examination in Part II must make written application to the Secretary's office not later than April 1, 1949

Candidates in military or naval service are requested to keep the Secretary's office informed of any change in address

Applications are now being received for the 1950 examinations Application forms and Bulletins are sent upon request made to the American Board of Obstetrics and Gynecology, Inc, 1015 Highland Building, Pittsburgh 6, Pennsylvania

SOCIETY MEETINGS AND CONFERENCES

JANUARY 7-APRIL 13 American College of Surgeons. Sectional Meetings. Page xi issue of December 23

MARCH 2-28 Consultation Clinics for Crippled Children in Massachusetts. Page 317 issue of February 24

MARCH 7-9 American Academy of General Practice. Page 276, issue of February 17

MARCH 8 Harvard Medical Society. Page 355

MARCH 8 New England Society of Anesthesiologists. Notice above.

MARCH 10 Evaluation of the Treatments of Arthritis. Dr Walter Bauer. Pentucket Association of Physicians. 8 30 p m. Haverhill

MARCH 15 South End Medical Club. Notice above.

MARCH 24 Cornell Medical Alumni Association. Page 276 issue of February 17

MARCH 28-APRIL 1 American College of Physicians. Page 158 issue of July 22

APRIL 2. American Academy of Pediatrics. Page 318 issue of February 24

APRIL 2-9 American Association of Industrial Physicians and Surgeons. Notice above

APRIL 5-8 Postgraduate Institute of Philadelphia County Medical Society. Page 240 issue of February 10

APRIL 14-17 American College of Allergists. Page 276, issue of February 17

DISTRICT MEDICAL SOCIETIES

HAMPDEN

APRIL 26 6 00 p m. Hotel Highland Springfield (Dinner Meeting) Convulsive Disorders. Dr Douglas T Davidson

HAMPSHIRE

MAY 4 Annual Meeting and Election of Officers.

MIDDLESEX EAST

MARCH 23

MAY 11

MIDDLESEX SOUTH

APRIL 20 Annual Meeting. Hotel Conventual, Cambridge

SUFFOLK

MAY 5 Censors' Meeting

WORCESTER NORTH

APRIL 27 Annual Meeting

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MARCH 10

FRIDAY, MARCH 11

*9 00 a.m.-12 00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital

*12 00 m. Clinicopathological Conference. Margaret Jewett Hall. Mt. Auburn Hospital. Cambridge

12 00 m.-1 00 p m. Clinicopathological Conference (Boston Floater Hospital). Joseph H. Pratt Diagnostic Hospital

1 30 p m. Tumor Clinic. Out Patient Department. Mt. Auburn Hospital. Cambridge

MONDAY MARCH 14

*12 15-1 15 p m. Clinicopathological Conference. Main Amphitheater. Peter Bent Brigham Hospital.

(Notices concluded on page xviii)

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Number 10

MANAGEMENT OF THE POTENTIALLY INFECTED OBSTETRIC CASE*

EDWARD G. WATERS, M.D.†

JERSEY CITY, NEW JERSEY

THE problem of potential infection in obstetrics is not new. Adam was the first man to attend a patient with potential infection in childbirth, and threat of infection is still the obstetrician's thankless heritage. Sepsis, which has been the leading cause of childbed death through incalculable ages, was uncontrolled until the first glimmering hopes were stirred by Alexander Gordon, Oliver Wendell Holmes, Charles White, of Manchester, and Ignaz Semmelweis.

When one considers the seemingly heroic efforts now required to reduce death rates by even 1 per cent, it is awesome to contemplate how the application of the simple principles enunciated by those pioneers lowered from 15 to 1 per cent the parturient death loss from sepsis alone. And this was before the revelations of Pasteur in 1879 established the groundwork, or the procedures of Lister became accepted and effective.

Today, many years later, puerperal sepsis still ranks among the most frequent causes of maternal death, despite the dangerously complacent attitude induced by the advent of the sulfonamides and antibiotic therapy. Although infection may be caused by any organism, four out of five are due to streptococci, and the most severe of these are the exogenous infections. The most frequent offenders, however, are the various nonhemolytic and some of the anaerobic streptococci, whose acquisition and acceleration of pathogenicity is dependent upon bacterial synergism in the presence of trauma, systemic disease, blood loss and other factors conducive to tissue destruction. The most dramatic and earliest reduction in patient loss came with control of exogenous infections. Cleanliness of the building, the bed and bedding, adequate ventilation, patient segregation, isolation of febrile patients, separation of personnel with or exposed to infections, adequate masking, surgical cleanliness of the obstetrician and aseptic vaginal examinations accounted for most of the improvement,

and these practices are still in effect. The persistence of puerperal fevers in spite of these precautions has led to an appreciation of the role played by endogenous infection and the manner in which organisms, in the presence of favoring conditions, assume degrees of pathogenicity that can be neither predicted nor calculated. Every post-partum and post-abortion patient has an open wound in the placental site. Most of the endogenous organisms not only are slow invaders but also break through the primary and local defenses with difficulty. The physiologic wound is well constructed by nature for its own protection. But lacerations, contusions and hematomas of the birth tract, retained secundines, blood loss, systemic disease and toxemia permit bacterial conversion to pathogenic status.

It is difficult to overestimate the enormous protection given the patient and the solace given the surgeon by the capacity of the sulfonamides, streptomycin and penicillin for control of infection. Deaths due to bacteremia from *Staphylococcus aureus* and *Streptococcus haemolyticus* have been practically eliminated in my experience. Without minimizing the beneficial effects of these substances, one must maintain a rational attitude toward present accomplishments. Chemotherapeutic attack is not sufficient for many of the infecting agents encountered. In many cases successful therapy is due to the maintenance of long and well established means for restoring physiologic balance in the patient under bacterial attack. In certain experimental work on peritonitis, also borne out by clinical observations, chemotherapy and the antibiotics are insufficient in themselves, once the disease is well established, to determine recovery. Survival is dependent upon the factors present before the onset of the disease or subsequent establishment of supportive measures to maintain the integrity of liver function, which is measurable by the capacity of the liver for normal prothrombin and fibrinogen production, requiring an adequate intake of protein and, through the avoidance of anoxemia, blood loss, hypotension and the like, a continuous supply of oxygenated blood. In any discussion of potential and actual infection

*Presented at the New England Postgraduate Assembly, Boston, Massachusetts, November 4, 1948.

†Assistant clinical professor of obstetrics and gynecology, Columbia University College of Physicians and Surgeons, New York City; division chief of obstetrics, Margaret Hague Maternity Hospital.

during labor and consideration of the ultimate consequences therein implied, the two shock-producing factors of trauma and infection are almost always concomitant. This association, in addition to blood loss, with the inevitable lack of available oxygen for the maintenance of basic tissue and organ metabolism makes for one of the most severe combinations imaginable. Acute and spreading peritonitis in itself is productive of a severe and most intractable form of shock. While all forms of infection in association with trauma and blood loss are harmful, peritoneal-cavity involvement is by all odds the worst. Thus the combination found in a traumatizing delivery worsens the patient's prospects if the peritoneal cavity need be opened and exposed to direct infection. In the occurrence of peritonitis, the bacterial endotoxins manifest powerful shock-producing properties in their poisons. Certainly, one may assume, on the basis of practical experience in the exhibition of chemotherapeutic agents in combating peritonitis, that these drugs act favorably against bacteria and endotoxins by affording a nonspecific protective action in the patient treated but are often ineffective against overwhelming infection. The vascular poisoning with resultant blood concentration and plasma loss produces septic shock and accounts for the well recognized efficacy of repeated blood transfusions in peritonitis. It hardly seems necessary to repeat that it is more important to *prevent* infection than to have to *treat* it and more important to *avoid* peritonitis than to hope to *check* it after its development. Whether infections in labor are handled by vaginal or abdominal operative procedures, the occurrence of trauma, blood loss and infection (which, alone and in combination, cause shock) interferes with the amount of oxygenated blood specifically needed for the organs and tissues for the maintenance of normal physiology. Hepatic function within physiologic range above all others must be maintained.

Infection during labor and the puerperium must therefore be regarded as wholly preventable if the patient is to be given maximal protection. This assumption is not invariably correct but must be so accepted to approach the irreducible minimum of patient loss.

Accordingly, I have included in management of infected labor some brief reference to the antecedent pregnancy, influencing factors in the labor, the preferential selection of manipulations for delivering the infected patient, and, finally, prevention of infection in the post-partum phase.

DURING PREGNANCY

It would be short-sighted indeed to regard obstetric infection as solely dependent upon omissions or commissions during labor and parturition. During the pregnancy itself, the obstetrician should prevent infection by lessening its occurrence and

minimizing its effects when it does occur. Without discussing this phase of the subject exhaustively, one may comment on some of the more obvious measures that can be taken. The patient's general nutrition, especially vitamin and protein balance, should be maintained throughout pregnancy, and especially in the last trimester. The blood picture must be known for the physician to detect and correct any existing anemia. Patients are routinely checked for Rh and blood type, and the record is made available on hospital admission. Early detection and treatment of cervicitis, pyelocystitis, vaginal infections and the like, as well as a search for signs of early toxemia, diabetes and systemic disease, any of which may undermine the patient's resistance, are part of good patient care.

During the last six weeks of pregnancy, control of vaginal infection includes prohibiting tub baths, intercourse and douching, and consideration of intravaginal application of sulfonamides in the presence of active vaginal infection. In the last part of pregnancy all primiparas in whom the head is unengaged at term are examined by x-ray to guide the obstetrician in his later management. All multiparas with histories of previous difficult deliveries should be scrutinized and given most careful x-ray study. It is important with the latter group to inquire exhaustively into the causes of previous stillbirths and neonatal deaths, which may offer a clue to prevention of recurrent fetal death or even greater catastrophe.

DURING LABOR

It is during labor that opportunities become most manifest and operative in determining the development of infection as well as the type of delivery. Repeated vaginal examinations, especially when there is a low placental implantation and when the membranes have been ruptured, are notable for increasing morbidity. Likewise, rectal examinations are not without danger inasmuch as adequacy involves protrusion of the rectovaginal septum by the examining finger through the cervix and against the presenting part. While in general it may truly be said that rectal examinations are preferable for routine checks during labor, there is no substitute in obstructive labor for a careful and complete vaginal examination done under aseptic precautions. This procedure will often completely reorient the operator and indicate a prompt decision on management. Abnormal positions and presentations can be most clearly made out, and these are prime factors in delayed labor with inherent septic possibilities. On this score, it should be noted well that disproportion and uterine inertia are almost inseparable and the presence of the latter bespeaks the existence of the former. This leads to prolonged labor, which, with or without ruptured membranes, means marked increase in morbidity and sepsis. Delayed labor due to midpelvic contraction is worse

than inlet contraction in that the condition is more easily overlooked, with a resultant longer labor. Failure of the head to engage or descend through the inlet is easily recognizable. In funnel-type pelvis, the obstetrician is often misled by early engagement, molding and a seemingly progressive although slow descent toward the pelvic floor. By the time he is aware of the true situation the life of the baby is often jeopardized, and he is put to it in deciding for the mother the safest means of ending labor.

When a patient has been in labor more than twelve hours or if the membranes without labor have been ruptured more than eighteen hours, it is my custom to start chemotherapy and antibiotic medication. Penicillin is most frequently used although often in combination with the sulfonamides, 40,000 units of penicillin is given initially, 300,000 units of procaine penicillin is given every twenty-four hours, and the dosage is maintained through the post-partum stage, being increased when indicated. Special regard must be given patients suffering from toxemia, chronic anemia or diabetes or who have lost blood from placenta previa or placental separation. The attendants are properly garbed and masked to control contamination. It has been estimated that 1 to 2 per cent of all patients are streptococcus carriers, and a higher percentage of the staff members are. Therefore precautions and preventive measures must be taken while the patient is in labor to obviate the likelihood of contamination. The treatment consists in overcoming any anemia that is present, replacement of blood that is being lost, treatment of any existing toxemia, assurance of sufficient fluid intake during labor, administration of adequate sedation to lessen the likelihood of too early interference in labor and strict observation of all of the standard obstetric principles. It is amazing, upon investigation for etiologic factors responsible for septic labor, how often such simple cardinal requirements for delivery as early appreciation of malpresentation and full dilatation of the cervix have been disregarded.

DURING PARTURITION

It follows when most of the foregoing precautions have been taken that infection in labor will not be a common sequel. However, in spite of this or because of some breach in judgment or management, the infected patient reaches the time when delivery is imminent or must be concluded. There can be little doubt that normal vaginal delivery is safest and best for both potentially and actually infected patients, since there is neither a sharp demarcation between the two nor any consistently positive method for indicating the transition from one to the other. Puerperal infection implies septic contamination of a wounded genital tract during labor or in the puerperium. Certainly, the normal transit

of a fetus through an undamaged birth tract ranks first in safety.

It should be remembered that cervical cultures from infected and normal patients do not differ significantly in bacterial content. Only when there is an overwhelming preponderance in the cervical or uterine culture of an organism found in the blood may it be considered significant. Some factor other than the mere presence of these endogenous infectors must be found to induce acquisition of virulence. The most important cause is trauma in a wide sense. The physiologic trauma induced by the separation of the placenta opens a large site for bacterial invasion. Except for contaminant organisms, the placental site is relatively well protected by nature against infection. A notable infector is the alpha-hemolytic streptococcus, for it is never endogenous and causes the worst infections (but it is most sensitive to chemotherapy). When one moves in any direction from normal vaginal delivery without trauma one increases the risk of puerperal sepsis. A close contender for safety to normal vaginal delivery is one accomplished by outlet forceps and perineotomy without other trauma. In what has been said thus far, there seems to be some concordance of opinion even among those who do battle over preferable ways for abdominal delivery.

Difficult forceps extractions are probably the greatest contributors to maternal deaths from sepsis. I do not mean that there is no place in obstetrics for mid-forceps deliveries or, for that matter, craniotomies on dead babies. I have indicated that mid-forceps in the presence of mid-pelvic contraction or funnel-type pelvis is dangerous and should be supplanted by better means for delivery. I believe their frequent use will disappear with widening indications for cesarean section and with more conservative treatment of the second stage of labor. Many of these patients with adequate sedation, general supportive treatment and judicious use of small doses of pitocin would deliver spontaneously if given enough time. Patients with adequate pelvis with dystocia due to malpresentation and deflection attitudes can be delivered by various means, and I prefer Kielland forceps rotation and extraction in many of these cases. The effectiveness of a mid-forceps application depends upon the degree of cephalic flexion present and the ability of the operator, in the absence of mid-pelvic contraction, to exert traction without deflection of the head. Better results from mid-forceps application will follow their disuse in patients with mid-pelvic and outlet contractions, and selective adoption of the proper forceps for the given pelvis and the special position of the vertex therein to be engaged. But the most important consideration of all, in the absence of definite dystocia, is reliance upon sedation and time. To put the matter in other words, one might say that no potentially or actually infected patient

should have a traumatizing vaginal delivery if the incidence of puerperal sepsis is to be diminished. If abdominal delivery is indicated, as often it must be by the very nature of the circumstances resulting in infected labor, there are two broad selections available. The first is cesarean section by one of the several types, and the second is cesarean section followed by hysterectomy, which is briefly discussed below, that there may be no mistake in my position.

Cesarean hysterectomy is not atraumatic. If the infected uterus is opened for the removal of the baby before it is extirpated, the result is not much better than that from a classic cesarean section. If a Porro type of operation is done, the baby's life is jeopardized. In any event a transperitoneal operation is performed, and the infected birth tract cut across, as indeed it must be, to remove the infected uterus. Sutures must then be placed

become so thoroughly adept at all the procedure, available that none of them would have to rationalize himself into the untenable position of chronically defending one type of procedure. With competence in all, judicious selection for the individual need will naturally follow, rather than autocratic pedantry exhibited by a one-operation department head.

Classic cesarean section was done for years for infection and obstruction in labor, with the ghastly results well known to everyone. The classic operation served its purpose and is respected for what it did when nothing better was available. It should never be done in infected labor and, in general practice, should never be done at all, except, for instance, as part of a cesarean section and hysterectomy for accompanying fibroids following clean labor with the patient at the end of her childbearing years. I believe the latter procedure is badly abused in young women with one or two children whose asymptomatic fibroids might better be treated later, if at all, by myomectomy. My experience with a large group of patients reveals the occurrence of fibroids in association with pregnancy as a rare indication for abdominal delivery. Excluding the irreconcilables, classic cesarean section should be considered as outmoded as vaccine therapy for pneumonia. Most obstetricians are in accord with the use of low-segment operations, especially with the transverse incision, for most patients coming to cesarean section. The question has recently arisen whether this operation with chemotherapy and the antibiotics is sufficient for patients who are potentially or actually infected. This will not easily or quickly be answered, and series offered with low mortality figures, of themselves, will not

TABLE 1 *Total Mortality, January 1, 1938, to January 1, 1948*

DATUM	No	PERCENTAGE
Total deliveries	67,959	—
Total deaths	120	0.17
Total cesarean sections	2,287	3.30
Deaths after cesarean section	17	0.74

through infected tissue at the vault after an appreciable amount of intraperitoneal tissue has been traumatized and exposed at least to local infection. I am not without experience with this procedure and consider myself capable of estimating its extent, although I do not perform it for infected patients. Indeed, publications dealing with morbidity and mortality of cesarean section and hysterectomy relate in the vast majority of cases to noninfected patients, although the data might erroneously suggest operations done for true puerperal infection. It seems, therefore, that the salutary effect of this operation is removal of a part of the infected genital tract, most notably the uterine placental site with its possible postoperative infection. In opposition are the dangers of a transperitoneal operation, often with incision into the infected uterus before extirpation and always with an incision across and through the infected birth tract. The almost universal acceptance that normal, nontraumatic vaginal delivery is the best way to deliver potentially and actually infected women certainly seems to negate the need for removing the uterus itself. If figures can be presented, as I believe they can, to show that abdominal delivery with retention of the uterus and without invasion of the peritoneal cavity is as safe as or safer than cesarean section combined with hysterectomy for infected patients, there should be little dispute about how these patients should be handled. All obstetricians, especially teachers of undergraduate obstetrics, should

TABLE 2 *Selective Data on Mortality, October, 1931, to January 1, 1945*

DATUM	No	PERCENTAGE
Total deliveries	75,238	—
Maternal deaths	200	0.26
Total cesarean sections	2,039	2.70
Deaths after cesarean section	29	1.42

suffice. It will take an accumulation of many deaths from puerperal infection and peritonitis following cesarean section with determination of the causes of the deaths and the technics of the operations to give the right answer. But at least it seems reasonable to believe that the transperitoneal approach cannot possibly be as safe as the extraperitoneal section, inasmuch as patients even now are dying from peritonitis in spite of adequate amounts of all the semispecific drugs available. Only when therapeutic measures available will save all patients who have peritonitis from dying, irrespective of the organism present, can one safely invade the peritoneal cavity to open

infected viscera, including the uterus. That day has not, as yet, arrived.

The data on mortality are presented in Table 1 and 2, and the relation of deaths to types of cesarean section in Table 3. Extraperitoneal cesarean section affords the safest of all abdominal approaches to the infected uterus. In an experience with 501 cases, with 1 death, or a mortality of 0.2 per cent, clean, potentially infected and grossly infected patients have been dealt with. The death that occurred was preventable on a technical basis. Sepsis due to direct invasion of the lymphatics and blood vessels without peritonitis was not seen. In this experience, dealing with more than 67,959 deliveries in the past ten years, 21 deaths from puerperal sepsis and peritonitis have occurred. The position of sepsis in relation to hemorrhage, toxemia and heart disease is indicated in Table 4. The subject of extraperitoneal cesarean section has been dealt with so often in the past few years that there is no need to reiterate all that has been said, but I believe, in view of the data submitted, that the onus is upon those who will neglect to use the best

placenta is extremely important. The use of oxytocics may be supplemented by use of bimanual compression if bleeding continues, as suggested nearly one hundred years ago by Hamilton. In any event the uterus *must not be packed*. In our clinic the intra-uterine pack is almost never used, and in the few cases in which it was, the patients died. In reading

TABLE 4 Causes of Death in Ten-Year Period among 67,959 Deliveries

CAUSE	PATIENTS WITH ABORTION	PATIENTS WITH VAGINAL DELIVERIES	PATIENTS WITH CESAREAN SECTIONS	TOTALS
Puerperal sepsis	5	10	2 { 1 Porro 1 lower transverse	15
Peritonitis	2	5 (2*)	2 (1 lower transverse*)	9 (3*)
Thrombosis	—	3	—	3
Embolism	—	7	—	7
Hemorrhage	—	11	3 { 1 Laizko 1 Porro 1 classic	14
Toxemia	—	9	3 (1†)	12
Heart disease	2	21	5 (3†)	28

*Peritonitis alone

†Post-mortem cesarean section

TABLE 3 Deaths in Relation to Type of Cesarean Section

TYPE OF SECTION	NO OF CASES	NO OF DEATHS	MORTALITY %
Transperitoneal and exclusion	1 406	13	0.92
Extraperitoneal	453	5	1.03
Waters supra-ovular	250	2	0.6
Laizko para-ovular	193	3	1.5
Classic	121	8	6.6
Porro (hysterectomy)	28	3	10.7

procedure indicated when there is existing or probable infection.

The matter of anesthesia in these patients is of importance, especially if there has been any shock-inducing blood loss. Blood loss during parturition is difficult to estimate, but my rule is to consider that the patient has lost one and a half times as much as the highest estimate given. In a recent case with ruptured uterus, 2750 cc. of whole blood was given in addition to plasma and other intravenous fluids, and yet twenty-four hours later the hemoglobin was 50 per cent. In any event, it is highly improbable that too much blood would be given these patients. The anoxemia associated with blood loss is furthered by any general anesthesia, and local anesthesia is generally not suitable in the presence of infection, 90 per cent of my patients are delivered with a low spinal anesthetic and *forced oxygen* is given the patient *during* and *subsequent* to the operation. All vomiting patients are lavaged before anesthesia is induced. All measures mentioned can be applied in any hospital, large or small.

Irrespective of the manner of terminating labor, the control of blood loss after delivery of the

maternal mortality reports one is struck by the recurring allegation variously phrased, "the situation became alarming, and it was decided to pack the uterus." There has been no death from hemorrhage, and no uterus has been packed in the last 25,000 deliveries in this clinic.

POST PARTUM

I have allowed a limited time for the post-partum phase, because respect for and adherence to the advice and principles thus far enunciated for pregnancy and parturition largely obviate the need of special concern after delivery. This does not minimize in any respect the great importance of the post-partum period in relation to infection. In the potentially and actually infected patient, irrespective of the manner of delivery, previously indicated therapy must be continued, and repeated checks made to obviate continuing or unrecognized secondary anemia. It is well to remember that careful inspection of the placenta will not eradicate occurrence of placental-remnant retention, with post-partum complications. Frequent offenders are small overlooked succenturiate lobes. Many deaths from puerperal fever follow nonfatal but severe hemorrhage in the post-partum period. Manipulations attendant upon its control, especially packing, and the debilitated state induced, permit the invasion and growth in virulence of organisms that normally would be inoperative. Late post-partum hemorrhages are generally severe and sudden and are due to incomplete separation of retained secundines or overlooked placental pieces. Bleeding, especially when accompanied by fever, signifies septic involvement of retained

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TABLE 1 Total Mortality, January 1, 1938, to January 1, 1948

DATUM	No	PERCENTAGE
Total deliveries	67,959	—
Total deaths	120	0 17
Total cesarean sections	2 287	3 30
Deaths after cesarean section	17	0 74

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TABLE 2 Selective Data on Mortality, October, 1931, to January 1, 1945

DATUM	No	PERCENTAGE
Total deliveries	75 238	—
Maternal deaths	200	0 266
Total cesarean sections	2 039	2 70
Deaths after cesarean section	29	1 42

suffice. It will take an accumulation of many deaths from puerperal infection and peritonitis following cesarean section with determination of the causes of the deaths and the technics of the operations to give the right answer. But at least it seems reasonable to believe that the transperitoneal approach cannot possibly be as safe as the extraperitoneal section, inasmuch as patients even now are dying from peritonitis in spite of adequate amounts of all the semispecific drugs available. Only when therapeutic measures available will save all patients who have peritonitis from dying, irrespective of the organism present, can one safely invade the peritoneal cavity to open

of the clinical and radiographic findings¹ Of the 18 cases, 3 were early, 6 moderately advanced, and the remainder greatly advanced Patients in the terminal stage of the disease were not included in this study

Activity was determined by the following criteria: the presence of objective signs of joint inflammation, including swelling, periarticular tenderness and limited mobility, and elevation of the erythrocyte sedimentation rate These were noted

dyscrasia Two may have received gold salts some time previously

All patients had been under our observation for at least three months prior to chrysotherapy and had received the customary basic therapeutic measures employed for this disease, without objective evidence of improvement

All were hospitalized for the course of intensive chrysotherapy No additional treatment, other than bed rest and simple orthopedic and physio-

TABLE 1 *Results of Chrysotherapy in 18 Cases of Rheumatoid Arthritis*

PATIENT	AGE	SEX	STAGE OF DISEASE	COMPOUND DOSEAGE	INITIAL RESPONSE	DURATION OF RESPONSE	FOLLOW-UP PERIOD	PRESENT STATUS*	REMARKS
				gm		mo	yr		
A. L.	57	M	Greatly advanced	Lauron 10.0	No improvement	—	24	No improvement	
R. A.	35	F	Moderately advanced	Lauron 10.0	No improvement	—	20	No improvement	
L. D.	67	F	Greatly advanced	Lauron 10.0	No improvement	—	19	Remission	Remission 6 mo after gold therapy
A. W.	58	M	Greatly advanced	Lauron 10.0	Slight improvement	14	18	Slight improvement	Marked functional improvement
C. S.	38	F	Greatly advanced	Lauron 10.0	Slight improvement	16	16	Slight improvement	Marked functional improvement
G. K.	45	F	Early	Lauron 10.0	No improvement	—	16	Remission	Remission 3 mo after gold therapy severe exfoliative dermatitis
M. A.	69	F	Early	Lauron 10.0	Remission	12	18	No improvement	Relapse 1 yr after completion of therapy mild exfoliative dermatitis
J. S.	55	F	Moderately advanced	Lauron 10.0	No improvement	—	18	No improvement	
M. C.	58	M	Greatly advanced	Lauron 3.0	No improvement	—	8	Slight improvement	Slight improvement 4 mo after gold therapy
H. B.	69	F	Greatly advanced	Lauron 3.0	No improvement	—	8	Slight improvement	Slight improvement 5 mo after gold therapy
P. H.	61	F	Greatly advanced	Lauron 3.0	No improvement	—	3	No improvement	
R. C.	67	F	Greatly advanced	Lauron 3.0	No improvement	—	3	No improvement	
A. T.	30	F	Greatly advanced	Lauron 1.1	No improvement	—	1	No improvement	
E. F.	40	F	Moderately advanced	Lauron 1.2	No improvement	—	12	Slight improvement	Slight improvement 6 mo after gold therapy
H. L.	41	F	Early	Lauron 1.1	No improvement	—	—	Unknown	
V. H.	51	F	Moderately advanced	Lauron 0.9	No improvement	—	12	No improvement	
A. M.	52	M	Moderately advanced	Solganol-B 1.0	No improvement	—	4	No improvement	
B. M.	45	F	Moderately advanced	Myochrysin 1.0	No improvement	—	2	No improvement	

*Based on therapeutic record and x-ray films of New York Rheumatism Association.

in all patients Most of the patients, in addition, presented a low-grade fever, a leukocytosis and a moderately severe anemia Some also had subcutaneous nodules or some variety of tenosynovitis

To exclude subclinical visceral complications, thorough laboratory data were obtained in all patients prior to therapy The blood studies consisted of complete cell counts, estimation of the hemoglobin and sedimentation rate, determination of the nonprotein nitrogen, sugar, uric acid, total protein, albumin-globulin ratio, total cholesterol and cholesterol esters and icteric index and the cephalin flocculation test Complete urinalyses were likewise performed Renal-function studies consisted of the concentration and dilution tests and the phenol-sulfonephthalein excretion Roentgenograms of the affected bones and joints were obtained in all cases Joint measurements and the ranges of motion of the affected articulations were determined before and after therapy

None of the patients treated gave a history of known toxicity to gold, showed any evidence of impaired renal function or suffered from any blood

therapeutic measures for the prevention of deformity, was permitted

While the patients were receiving aurotherapy, complete blood counts, including platelets, and urinalyses were performed twice weekly The erythrocyte sedimentation rate was determined every two or three weeks

Sixteen patients received lauron, 1 aurothio-glucose (solganol-B oleosum), and 1 gold sodium thiomalate (myochrysin) for comparative information

The dosage of gold salts varied from 0.9 to 10 gm The entire quantity was given intramuscularly, in divided, ascending doses twice weekly, for six to eight weeks Eight patients received a total amount of 10 gm during this period, 4 were given 3 gm, and the remainder, 0.9 to 1.2 gm Each of the patients treated with solganol-B oleosum and myochrysin received 1 gm of these respective gold salts Several patients on intermediate total courses of lauron, and 1 on a 1-gm course of gold sodium thiosulfate, have been excluded because they did not remain in the hospital long enough

placental segments The blood must be replaced, Fowler's position employed to ensure adequate genital drainage, and the vaginal and perineal wounds inspected if morbidity persists These patients are all given oxytocics, preferably ergotrate, routinely the first three days post partum to hasten involution and to close off venous and lymphatic channels of spread Adequate fluid and vitamin intake is ensured, the bladder is kept empty, the blood picture is constantly checked, blood cultures and urine specimens are obtained if the fever continues and early ambulation is encouraged when the infection is under control It should be recalled that increased trauma with tissue autolysis increases prothrombin formation and platelet production and thereby increases the possibility for peripheral and unfavorable clot for-

mation The use of heparin and dicumarol, in sequence or independently, is indicated to check thrombus formation or spread

CONCLUSIONS

Puerperal sepsis often has its beginnings in states and conditions during pregnancy that enhance its development In the healthy patient going into labor, blood loss, toxemia and trauma, incident to or subsequent upon prolonged labor, inertia and difficult delivery, are the most important factors in its production The treatment of infection or obstruction in labor demands individual consideration of all the possibilities in the patient's interest, normal, nontraumatic vaginal delivery and extra-peritoneal cesarean section offering, by all odds, the most favorable prospects

INTENSIVE CHRYSOTHERAPY (WITH LAURON) IN RHEUMATOID ARTHRITIS*

H HAROLD FRIEDMAN, M D,† AND OTTO STEINBROCKER, M D ‡

NEW YORK CITY

THIS report presents the results obtained with intensive chrysotherapy in the treatment of 18 patients with rheumatoid arthritis The purpose of the study was to investigate the usefulness of large quantities of gold salts administered over a relatively short period In spite of the limited number of cases treated, our observations are reported for whatever significance they may have, since we do not plan to continue the investigation

Although there has been a trend in this country toward relatively small doses of gold salts, intensive treatment with gold compounds was employed for several reasons The manufacturer of the preparation used in this study proposed an investigation of the possibilities of intensive dosage under hospital conditions because a single dose of 5 gm administered erroneously to a patient by her physician had resulted in some apparently rapid benefit and had not been attended by untoward reactions, because a short period of intensive treatment in a hospital, if found to be safe and practical, might be advantageous for patients unable to submit to the conventional long-term treatment, and because aurothioglycanilide (lauron), being insoluble and therefore more slowly absorbed, might provide, with intensive doses, a store of gold in the

body that would be released for a long period to maintain beneficial effects The fact that large doses of gold salts had been regularly given and are still advocated by some European workers gave us some reassurance Furthermore, we had used lauron for some time in small doses and found the frequency of toxicity, in a limited series of cases, to be no greater and generally milder than that of soluble gold preparations

Although we had not been impressed with the final effectiveness of conventional doses of gold salts, the use of large doses, if found safe, appeared to be a worthy test of the efficacy of chrysotherapy, at least of lauron, in any suppressive action on the rheumatoid process or palliation of symptoms It so happened that, at about the time we were contemplating this study, a patient with active rheumatoid arthritis, who had experienced a number of failures with other modes of therapy, volunteered in his desperation to undergo "any experiment that might help in the slightest way" He consented to the regime proposed, and his was the pilot study Ten gm of lauron was administered to him in ascending doses over an eight-week period without complication His dosage schedule was followed in other patients who received this amount

METHODS OF STUDY

Eighteen patients with active rheumatoid arthritis in various stages of the disease were selected for treatment They were classified as presenting the early, moderately advanced or greatly advanced stage, according to the severity

*From the Medical Service and Arthritis Clinic of the Fourth Division (New York University) Bellevue Hospital
This study was aided by a grant from the Endo Company which also supplied the material

†Assistant in medicine University of Colorado Medical Center assistant attending physician Denver General Hospital associate attending physician, National Jewish Hospital, Denver Colorado formerly fellow in medicine, New York University College of Medicine and assistant resident in medicine Fourth Division (New York University) Bellevue Hospital

‡Associate clinical professor of medicine New York University College of Medicine, attending physician Bellevue Hospital physician in charge Arthritis Clinic, Fourth Division Bellevue Hospital

and showed slightly decreased signs of rheumatoid activity beginning four, five and six months respectively after completion of gold therapy in what again might be regarded as "delayed responses."

The toxic reactions in this series consisted only of one severe and one mild local exfoliative dermatitis. The patient with the severe exfoliative dermatitis, after a stormy course, made a complete recovery.

Eosinophilia of varying degree was encountered in nearly all these patients while they were under treatment. The count ranged from 3 per cent to 17 per cent in 15 of them. Two cases with eosinophil counts up to 22 per cent and 43 per cent developed, respectively, a mild and a severe exfoliative dermatitis. A high degree of eosinophilia may be a premonitory sign of impending toxicity, although one patient exhibited a count of 29 per

It may not be irrelevant to mention at this point that even the better results of the small doses are statistically close to those reported by Short and Bauer⁴ with simple medical and orthopedic measures. It is therefore doubtful whether aurothioglycanilide in either of these groups has shown promise of long-range benefits superior to those observed after general medical measures. However, a suggestively greater number of initial remissions following completion of chrysotherapy among patients receiving smaller doses can have been only of questionable significance in such a small number of patients for the length of time treated.

In our very limited series of cases, large doses of lauron did not prove unduly toxic, but it must be stated that one of us (O. S.) has observed elsewhere severe skin reactions from conventional doses of aurothioglycanilide. In fact, in our small series

TABLE 4 Gold Levels* in Blood, Urine and Feces †

PATIENT	PREPARATION	TOTAL DOSE	AVERAGE GOLD LEVEL IN WHOLE BLOOD DURING LATTER PART OF THERAPY	GOLD LEVEL IN WHOLE BLOOD ONE WEEK AFTER COMPLETION OF THERAPY	AVERAGE GOLD IN URINE (TWENTY-FOUR HOUR EXCRETION)	AVERAGE GOLD IN FECES (TWENTY-FOUR HOUR EXCRETION)
		gm	microgm. per 100 cc	microgm. per 100 cc	microgm	microgm
A. M.	Solganol B oleosum	1.0	0.156	0.122	0.167	0.100
B. M.	Myochrynine	1.0	0.253	0.265	0.261	0.158
A. T.	Lauron	0.9	0.132	0.120	0.035	0.026
A. C.	Lauron	3.0	0.028	0.105	0.039	—†
A. W.	Lauron	10.0	—†	1.4	—†	—†
G. K.	Lauron	10.0	—†	1.6	—†	—†
C. S.	Lauron	10.0	—†	3.4	—†	—†

*Spectrographic analysis (accuracy of method, ± 15 per cent)

†Determinations by Charles J. Umberger, Ph.D.

‡No determinations done.

cent without adverse symptoms. Further detailed experience with eosinophilia in chrysotherapy will be reported separately.³

DISCUSSION

From the results obtained in a limited series of cases, according to our standards of evaluation, it appears that intensive gold therapy with large or accelerated doses of lauron offers no advantage over treatment with smaller doses in the usual manner. The number of patients is admittedly too small to permit final appraisal of this form of treatment, although it does provide a highly suggestive index to its effectiveness. For comparison, we are including the results obtained by us with the usual doses of lauron in 20 patients with this disease (Table 3). In this group the total dosage ranged from 1 to 3 gm, given in one to three courses for six months to two and a half years, together with a follow-up period of from two and a half to four and a half years. If it is permissible to draw tentative deductions concerning the trend of response in such small groups, the figures suggest, surprisingly enough, that the immediate results with lesser doses are better than those with massive dosage.

all toxic reactions with usual and large doses of this substance consisted of cutaneous manifestations. An unpredictable personal factor probably is involved in many toxic reactions and fortunately did not appear, except in 1 case. This patient developed a severe exfoliative dermatitis. Since this complication may occur with small doses of gold, it cannot be ascribed merely to the large amounts employed.

On the whole the results obtained with intensive and accelerated chrysotherapy in this relatively small number of cases have been poorer than those reported by others with lauron⁵⁻⁷ and with other gold salts. Since aurothioglycanilide is an insoluble salt, the question then arises whether it is absorbed in sufficient quantities to be effective, particularly when given so rapidly and in massive doses. The fact is that the blood levels attained by the large doses of lauron, estimated by spectrography, were within the ranges of those produced by much smaller quantities of the other gold compounds, or they showed a rise in proportion to the amount of this salt administered (Table 4), at least one week after the completion of therapy. While it is true that roentgenograms taken by us, in some cases as long as two years after lauron therapy, have

for sufficient therapy It was planned at first to treat a larger group given varying total courses evenly distributed among the series The outcome of treatment at this point, however, led to the termination of the study Maintenance doses were not employed afterward for obvious reasons Patients were included consecutively without any attempt at selection according to the severity of the disease, except for terminal cases An explana-

still active The 2 patients whose rheumatoid activity slightly decreased have maintained that improvement so far Both have also shown marked improvement in functional capacity Semi-invalids prior to treatment, both have subsequently been able to conduct their occupations satisfactorily in spite of persistent signs of rheumatoid activity One patient with early rheumatoid arthritis was unimproved after termination of her course of 10

TABLE 2 Results of Intensive Chrysotherapy in 18 Patients with Active Rheumatoid Arthritis

STAGE OF DISEASE	NO OF CASES	INITIAL RESPONSE				FINAL EVALUATION*			
		GRADE I†	GRADE II†	GRADE III†	GRADE IV†	GRADE I†	GRADE II†	GRADE III†	GRADE IV†
Stage I (early)†	3	2‡	0	0	2	1	0	0	2
Stage II (moderately advanced)†	6	0	0	2	4	0	0	1	4
Stage III (severe)†	9	1‡	0	0	9	1	0	4	4
Totals	18	3‡	0	2	15	2	0	5	10

*No follow-up study was available on 1 patient on the others the follow up period was 8 to 18 months
†Classification of stages and grades (I — complete remission II — major improvement, III — slight or minor improvement, and IV — no improvement) of response according to criteria of the New York Rheumatism Association The response was re-evaluated from results on our therapeutic score card in some cases
‡One patient had early disease in remission 3 months after completion and another had greatly advanced disease with complete remission 6 months after the end of treatment.

tion of the character of the treatment was given, after which each one was required to sign a permit

RESULTS

The results obtained are given in Table 1 and 2 Evaluation of the response to treatment was carried out by means of the criteria provided in our therapeutic score card,² which, aside from a few minor differences, is in close accord with the therapeutic criteria adopted by the New York Rheumatism Association Late in the study these therapeutic

gm of lauron Three months later a widespread exfoliative dermatitis developed, and simultaneously there was a complete remission of the arthritic picture It might be questioned whether this remission can be credited to gold therapy since it occurred so long after aurotherapy was completed For thirteen months this patient so far has remained in complete remission, except for a moderately elevated erythrocyte sedimentation rate, 40 mm in 1 hour (Westergren method) —

TABLE 3 Results in 20 Cases of Rheumatoid Arthritis Treated with the Usual Doses of Lauron

STAGE OF DISEASE	NO OF CASES	INITIAL RESPONSE				FINAL EVALUATION*			
		GRADE I†	GRADE II†	GRADE III†	GRADE IV†	GRADE I†	GRADE II†	GRADE III†	GRADE IV†
Stage I (early)†	10	5	1	2	2	2	0	3	6
Stage II (moderately advanced)†	4	1	0	2	1	0	1	1	2
Stage III (severe)†	6	1	0	3	2	0	0	3	2
Totals	20	7	1	7	5	2	1	7	10

*The follow-up periods ranged from two to four and a half years (recently completed) recurrences in Grade I shifted (noted in three to thirty six months) There were 3 toxic reactions none of which were serious
†The classification of stages and grades of response re-evaluated from results on our therapeutic score card to therapeutic criteria of the New York Rheumatism Association was the same as that outlined in Table 2.

criteria were applied simultaneously with the therapeutic score card Of the 18 patients observed, 1 with early rheumatoid arthritis was in complete remission at the end of the course of gold therapy Two patients in the greatly advanced stage showed slight improvement in the signs of rheumatoid activity, and the remainder were unimproved or worse when treatment was terminated The patient in whom remission was observed relapsed one year later, and her disease process is

“greatly improved,” according to the new therapeutic criteria Another patient, who was unimproved after chrysotherapy, had a complete remission six months later Her disease process has remained clinically inactive for twelve months It is more debatable in this case whether the good effect can be attributed to the therapy as a “delayed response” postulated for this type of gold preparation Three patients who initially were unimproved developed somewhat better functional capacity

SUBTOTAL GASTRECTOMY OR VAGOTOMY FOR PEPTIC ULCERATIONS*

Early Results and Postoperative Symptoms

RICHARD WARREN, M D,† AND EDMUND C MEADOWS, M D ‡

WEST ROXBURY, MASSACHUSETTS

EVER since the operation of vagotomy has been used in the treatment of peptic ulcer numerous reports have appeared analyzing the early postoperative results. The first of these that has made a direct comparison between the results of this operation and of those of subtotal gastrectomy has been that of Allen.¹ He found good results in 85 per cent of the gastrectomy groups and 87 per cent of the vagotomy, fair results in 7 per cent and 6 per cent, and poor results in 8 per cent and 7 per cent of the two groups respectively. The postoperative mortality in the gastrectomy group was 2 per cent, in the vagotomy group it was zero. Allen concluded that the early and interim results from the operation of vagotomy showed that the number of patients who did not fare satisfactorily after operation was roughly the same as that in the subtotal gastrectomy group. He outlined clinical criteria for the use of the two operations to serve as a temporary guide until more information on these operations should be acquired. Although the follow-up period of our patients who have had vagotomy is still extremely short we have been tempted to make a similar comparison between the operations and to check our results against those of Allen and other observers in this field.²⁻⁶

REVIEW OF THE LITERATURE

Follow-up studies on gastric surgery⁷⁻¹¹ have logically divided unfavorable results into three categories: mortality, incidence of recurrent (stomal) ulcer and incidence of unfavorable side effects — that is, easy gastric filling, nausea and vomiting, food intolerance, dumping syndrome, failure to gain weight, poor appetite and anemia.

Mortality

Reported mortality rates following subtotal gastrectomy have fallen during recent years⁷⁻¹⁰⁻¹²⁻¹³ to a level of 1 to 3 per cent. The chief cause of this mortality has been technical failure properly to manage closure of the duodenal stump.¹⁴ Careful management and operative technic should, therefore, enable this figure to approach zero.

The mortality following vagotomy has been calculated as 1.6 per cent from a total of 481 cases

(Table 1). The causes of these deaths are listed in Table 2. With the exception perhaps of the case of aspiration pneumonia, they have been sudden and unpredictable.

Recurrences

The incidence of stomal ulcer following high subtotal gastrectomy for duodenal ulcer is between

TABLE 1 Mortality Following Vagotomy

AUTHOR	NO OF CASES	NO OF DEATHS
Dragstedt et al. ¹⁵	212	1
Grimson et al. ¹⁶	57	1
Walters et al. ¹⁷	83	5
Thorek ¹⁸	25	5
Moore ¹⁹	74	0
Warren and Meadows	50	0
Totals	481	8 (1.6%)

3 and 10 per cent¹⁰⁻¹⁹⁻²² or considerably less than the figure of 10 to 30 per cent reported for that following gastroenterostomy.²⁰

The early incidence of persistence or recurrence of old ulcers or the occurrence of new ulcers following vagotomy has been calculated as 4.2 per cent

TABLE 2 Causes of Death after Vagotomy Reported in the Literature

CAUSE OF DEATH	NO. OF CASES
Aspiration pneumonia	1
Gastric dilatation	1
Perforation	3
Cardiovascular accidents	3
Shock	1

from a total of 427 cases (Table 3). In the cases reported as recurrences by Dragstedt and his associates¹⁵ the insulin test of Hollander, in which insulin hypoglycemia is used to provoke a vagus-mediated gastric secretion, showed the operations to have been technically incomplete. In the study of Walters et al.¹⁶⁻¹⁷ and in ours this has not been uniformly true. In 2 cases from the composite group new gastric ulcers developed in the postoperative period, vagotomy having been done for duodenal ulcer. A possible explanation for such an occurrence has been offered.²⁵

*Presented at the annual meeting of the New England Surgical Society, New Haven, Connecticut, October 1, 1948.

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‡Chief Surgical Service, Veterans Administration Hospital, associate in surgery, Harvard Medical School.

§Resident in surgery, Veterans Administration Hospital.

shown the presence of radiopaque material in the soft parts, spectrographic analyses of gold in the blood and excreta during the course of treatment, and afterward, in some of the patients in this series have shown gold levels within proportionately lower but comparable therapeutic ranges reported with other gold preparations.^{8,9} Chemical studies of gold in blood, urine and feces also were carried out in almost every case. Owing to the uncertainty among members of the Toxicology Department, where the analyses were done, regarding the accuracy and reliability of these determinations, it was deemed advisable not to include them.*

SUMMARY AND CONCLUSIONS

The results of intensive and accelerated gold therapy in 18 patients with active rheumatoid arthritis in various stages of the disease are reported. Sixteen patients were treated with aurothioglycanilide (lauron), one with aurothioglucoase (solganol-B oleosum) and another with gold sodium thiomalate (myochrysine). The dosage ranged from 0.9 to 10 gm administered over a period of six to eight weeks in each case.

The initial results, immediately after completion of the gold therapy, were as follows: complete remission of signs, 1 case; slight improvement, 2 cases; and no improvement, 15 cases. The patient who went into complete remission subsequently relapsed.

*Spectrographic and chemical analyses were conducted through the courtesy and interest of Drs. Alexander O. Gettler and Charles J. Umberger.

Complete remission of symptoms and signs occurred in 2 other patients three and six months respectively after intensive chrysotherapy, and each has maintained that status for thirteen months. These may be regarded as initial, "delayed responses, but may have been spontaneous."

The use of large doses of gold salts over a short period in this series of patients was not attended by an increased number of reactions, but the group is too small for any positive deductions regarding the safety of intensive chrysotherapy.

Large and accelerated doses of aurothioglycanilide in these cases did not exert impressive palliative or suppressive effects on the signs and symptoms of rheumatoid arthritis.

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SUBTOTAL GASTRECTOMY OR VAGOTOMY FOR PEPTIC ULCERATIONS*

Early Results and Postoperative Symptoms

RICHARD WARREN, M.D.,† AND EDMUND C MEADOWS, M.D.‡

WEST ROXBURY, MASSACHUSETTS

EVER since the operation of vagotomy has been used in the treatment of peptic ulcer numerous reports have appeared analyzing the early postoperative results. The first of these that has made a direct comparison between the results of this operation and of those of subtotal gastrectomy has been that of Allen¹. He found good results in 85 per cent of the gastrectomy groups and 87 per cent of the vagotomy, fair results in 7 per cent and 6 per cent, and poor results in 8 per cent and 7 per cent of the two groups respectively. The postoperative mortality in the gastrectomy group was 2 per cent, in the vagotomy group it was zero. Allen concluded that the early and interim results from the operation of vagotomy showed that the number of patients who did not fare satisfactorily after operation was roughly the same as that in the subtotal gastrectomy group. He outlined clinical criteria for the use of the two operations to serve as a temporary guide until more information on these operations should be acquired. Although the follow-up period of our patients who have had vagotomy is still extremely short we have been tempted to make a similar comparison between the operations and to check our results against those of Allen and other observers in this field.²⁻⁶

REVIEW OF THE LITERATURE

Follow-up studies on gastric surgery⁷⁻¹¹ have logically divided unfavorable results into three categories: mortality, incidence of recurrent (stomal) ulcer and incidence of unfavorable side effects — that is, easy gastric filling, nausea and vomiting, food intolerance, dumping syndrome, failure to gain weight, poor appetite and anemia.

Mortality

Reported mortality rates following subtotal gastrectomy have fallen during recent years^{7, 10, 12, 13} to a level of 1 to 3 per cent. The chief cause of this mortality has been technical failure properly to manage closure of the duodenal stump.¹⁴ Careful management and operative technic should, therefore, enable this figure to approach zero.

The mortality following vagotomy has been calculated as 1.6 per cent from a total of 481 cases

(Table 1). The causes of these deaths are listed in Table 2. With the exception perhaps of the case of aspiration pneumonia, they have been sudden and unpredictable.

Recurrences

The incidence of stomal ulcer following high subtotal gastrectomy for duodenal ulcer is between

TABLE 1 Mortality Following Vagotomy

AUTHOR	NO OF CASES	NO OF DEATHS
Dragstedt et al. ¹⁵	212	1
Grimson et al. ⁸	57	1
Walters et al. ^{16, 17}	85	3
Thorelli ¹⁸	25	3
Moore ¹⁹	74	0
Warren and Meadows	50	0
Totals	481	8 (1.6%)

3 and 10 per cent^{10, 19-22} or considerably less than the figure of 10 to 30 per cent reported for that following gastroenterostomy.²⁰

The early incidence of persistence or recurrence of old ulcers or the occurrence of new ulcers following vagotomy has been calculated as ± 2 per cent

TABLE 2 Causes of Death after Vagotomy Reported in the Literature

CAUSE OF DEATH	NO OF CASES
Aspiration pneumonia	1
Gastric dilatation	2
Perforation	2
Cardiovascular accidents	2
Shock	1

from a total of 427 cases (Table 3). In the cases reported as recurrences by Dragstedt and his associates¹⁵ the insulin test of Hollander, in which insulin hypoglycemia is used to provoke a vagus-mediated gastric secretion, showed the operations to have been technically incomplete. In the study of Walters et al.^{16, 17} and in ours this has not been uniformly true. In 2 cases from the composite group new gastric ulcers developed in the postoperative period, vagotomy having been done for duodenal ulcer. A possible explanation for such an occurrence has been offered.²³

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Unfavorable Side Effects

The difficulty of evaluating unfavorable side effects following gastrectomy was shown by St John and his co-workers,¹¹ who stated that almost 20 per cent of people without ulcers have, according to their answers to a follow-up questionnaire, symptoms that would place them in an unsatis-

TABLE 3 Recurrent or Persistent Ulcer after Gastrectomy

AUTHOR	NO OF CASES	NO OF ULCERS
Dragstedt et al ¹⁸	160	5
Grimson et al ³	57	1
Walters et al ^{16, 17}	50	3
Moore ^{4, 5}	74	1
Harkins et al ¹¹	36	4
Colp ²⁴	20	1
Warren and Meadows	30	3
Totals	427	18 (4.2%)

factory group Jordan⁹ found that 60 per cent of patients had gastrointestinal symptoms of some sort after gastric resection for duodenal ulcer. St John et al¹¹ stated that approximately half the unsatisfactory results were due to features other than recurrent ulceration. Allen and Welch⁷ noted persistent gastrointestinal symptoms in a third of the patients. The most frequent residual symptom was that of a "small stomach,"—that is, the inability to eat a full meal, and discomfort, gas or

syndrome in 56 per cent of 500 cases. Contrary to popular opinion, they found that the syndrome persisted in 21 of 24 cases, after periods of five to eight years.

Hypochromic anemia following subtotal gastrectomy occurs in between 5 per cent and 9 per cent of cases.²⁸ Macrocytic anemia is very rare.²⁹ Anemia is more common in women than men³⁰ and is relatively unresponsive to iron and liver therapy, being best relieved by vigorous dietary means.³¹

The most detailed analysis of the unfavorable side effects following vagotomy has been made by Grimson and his co-workers,³ who in a series of 57 cases reported uncomfortable gastric fullness in 40, gas pains in 38, trouble with swallowing in 21, temporary diarrhea in 20 and episodes of acute epigastric pain in 6. The authors report, on the other hand, that 50 of the 57 patients gained weight postoperatively, and 53 were able to pursue gainful employment. Moore^{4, 5} has reported that although some symptoms, usually fullness, were present in 56 per cent of his patients, 87 per cent were satisfied with the result of the operation. A composite summary of this review of the literature is given in Table 4. It has served as a baseline for this study.

MATERIAL

Source

During the 24 months, July 1, 1946, to June 30, 1948, out of 494 patients admitted to the West

TABLE 4 Reported Results Following Partial Gastrectomy for Duodenal Ulcer Contrasted with Those Following Vagotomy for Duodenal or Stomal Ulcer

APPROXIMATE COMBINED RESULTS AFTER PARTIAL GASTRECTOMY				APPROXIMATE COMBINED RESULTS AFTER VAGOTOMY			
AUTHOR	MORTALITY	RECURRENT OF ULCER	UNFAVORABLE SIDE EFFECTS	AUTHOR	MORTALITY	RECURRENT OF ULCER	UNFAVORABLE SIDE EFFECTS
	%	%	%		%	%	%
Allen and Welch ⁷ Lahey ¹² St. John et al ¹¹	{ 1-3			Dragstedt et al ¹⁸ Grimson et al ³ Walters et al ¹⁷ Thorell ¹⁴ Moore ^{4, 5} Warren and Meadows	{ 1-6		
Allen and Welch ⁷ Kiefer ¹⁰ Lewisohn ²⁰ Mage ¹¹ Matzer ² Rienhoff ¹⁹		{ 3-10		Dragstedt et al ¹⁸ Grimson et al ³ Walters et al ¹⁷ Moore ^{4, 5} Harkins and Hooker ¹¹ Colp ²⁴ Warren and Meadows		{ 4-2	
Allen and Welch ⁷ Jordan ⁹			{ 30-60	Grimson et al ³ Moore ^{4, 5}			{ 50-75

nausea after eating. They found that more patients lost weight than gained, but that symptoms referable to this were unusual. The average weight loss was nearly twice as high in women as in men.

The dumping syndrome, or "dumping stomach," so named by Mix²⁶ in 1922, represents perhaps a more distressing side effect of gastrointestinal anastomosis than any other. Custer, Butt and Waugh²⁷ found typical features of this postprandial

Roxbury Veterans Hospital with peptic ulcer (Table 5). 120 operations were performed with the purpose of curing the ulcer (Table 6). Eighty-nine of these operations were subtotal gastrectomies, 28 were vagotomies, and 3 were gastroenterostomies.

The selection of patients for operation was based upon their failure to be controlled on medical therapy. Medical treatment was deemed to have failed if pain could not be alleviated in the hospital.

Moreover, if outside the hospital under normal environmental conditions, a patient repeatedly became uncontrollable in spite of proper dietary discipline, he was selected for operation. Other indications of failure of medical treatment were repeated massive hemorrhages in a young man or one or more massive hemorrhages in an older one, and pyloric obstruction of a cicatricial sort. In general, the older the patient, the more seriously we have regarded the symptoms of hemorrhage.²² It is in this group that we have adopted the policy of urgent operation if the hemorrhage persists or recurs.²³

The patient with low intelligence, compensation neurosis or emotional factors that make it impossible for him to follow a proper medical regime presents a special problem. Results here are relatively poor regardless of the treatment used. In our clinic we have been more prone to treat these patients by surgical than by medical methods. This attitude has been adopted for the following reasons. The readmission of such patients to the hospital is frequent. Their complaints, although often unconvincing, can never be put aside as inconsequential as long as an active ulcer is shown by x-ray examination. After operation, which removes or heals the ulcer, although the patient's previous social and economic existence is seldom improved

uncertainties produced by conflicting x-ray studies, such as whether the ulcer was on the gastric or duodenal side, whether there were unusual duodenal deformities and occasionally whether an ulcer was present at all, obviously poor mechanical situations resulting from ill advised previous surgical procedures, such as high anterior gastroenterostomy,

TABLE 5 *Types of Peptic Ulcer, Veterans Administration Hospital, West Roxbury, Massachusetts*

TYPE OF ULCER	NO. OF PATIENTS	NO. OF DISCHARGES
Duodenal	414 (83.9%)	475 (83.1%)
Gastric	55 (11.1%)	65 (11.4%)
Marginal	10 (2.0%)	14 (2.4%)
Peptic	10 (2.0%)	12 (2.1%)
Duodenal and gastric	5 (1.0%)	5 (0.9%)
Totals	494	569

and pyloric obstruction. All patients not falling under these contraindications were submitted to vagotomy.

A follow-up study was made on 54 patients who had received subtotal gastrectomy and on 22 patients who had received vagotomy. These patients were unselected and comprised all those who could be communicated with and who had been

TABLE 6 *Surgery for Peptic Ulcer, Veterans Administration Hospital, West Roxbury, Massachusetts*

OPERATION	CASES OF DUODENAL ULCER	CASES OF GASTRIC ULCER	CASES OF STOMAL ULCER	TOTALS	PATIENTS RECEIVING DEFINITIVE SURGERY	NO. OF DEATHS
Partial gastrectomy						
One stage	55	26	0	81		
First stage	8	1	0	9		
Second stage	7	1	0	8		
Vagotomy					89*	5 (5.5%)
Transthoracic	11		5	14		
Transabdominal alone	4		1	5		
Transabdominal and gastric intestinal anastomosis						
Pyloric plasticity	5			5		
Posterior gastroenterostomy	4			4		
Posterior gastroenterostomy	3			3	28	0
Repair of perforation	23			23	5	0
Totals	120	28	4	152	120†	5 (2.5%)

*Completed resections

†Or 21 per cent of discharged ulcer patients (569)

the fear of serious complications such as perforation and hemorrhage is diminished and a complex clinical picture simplified.

In the group of patients chosen for surgical procedures we made a further selection for the operation of vagotomy by considering all patients suitable for vagotomy who did not have the following contraindications:²⁵ recent massive hemorrhage in patients over forty-five years of age, or active bleeding at the time of operation at any age, diagnostic

operated upon during the first eighteen months of the two-year period. The length of the intervals between operation and examination varied between four and twenty-four months.

Age

Because of the manner of selecting the two groups of patients there was considerable disparity in their average age. The ages of the gastrectomy patients ranged from twenty-three to sixty-six years and

averaged forty-nine years and one month. Those of the vagotomy patients ranged from twenty-three to fifty-two years, with an average of thirty-four years.

Mortality

There were 3 deaths in the gastrectomy group. A subtotal gastrectomy for gastric ulcer was followed by death due to pneumonia and paralytic ileus. A second patient succumbed to retroperitoneal sepsis from a leakage from the duodenal

continuity of at least some of the fibers of the right vagus.

At this early date there have been no proved recurrent ulcerations among the 54 patients whom we have examined since subtotal gastrectomy. One of the patients experienced ulcer type of pain, but barium meal and gastroscopy showed no ulcer and the pain disappeared after reassurance. Three others had epigastric pain unlike the previous ulcer pain. After making this study we have heard that 1 of the 2 patients receiving subtotal gastrectomies who did not respond to our request for a follow-up interview is at another hospital with an anastomotic ulcer. Two patients from the vagotomy group, in addition to the 3 who had recurrent ulcer, had some mild epigastric pain, but gastrointestinal x-ray films showed no active ulceration.

TABLE 7 Summary of Unfavorable Side Effects in 76 Patients Who Received Partial Gastrectomy or Vagotomy *

SIDE EFFECT	PARTIAL GASTRECTOMY		VAGOTOMY	
	NO. OF PATIENTS	PERCENTAGE	NO. OF PATIENTS	PERCENTAGE
Pain	3	5.5	6	28.0
Vomiting	9	16.6	9	31.0
Poor appetite	9	16.6	6	28.0
Diarrhea	4	7.4	4	18.1
Restricted diet	18	33.3	5	22.7
Dumping syndrome	25	46.3	4	18.1
Easy fatigue	21	38.8	5	22.7
Poor economic result	9	16.6	1	4.5

*The average gain in weight was 79 pounds for patients receiving gastrectomy and 5 pounds for those receiving vagotomy. The average hemoglobin in the two groups was, respectively, 79 and 87.5 per cent.

Unfavorable Side Effects

Table 7 summarizes the incidence of unfavorable side effects in the two groups. Pure gastrointestinal symptoms such as pain, vomiting and diarrhea tend to be more prominent in the vagotomy group. Other symptoms such as poor appetite, fatigue and dumping syndrome predominate in the gastrectomy group.

General Appraisal

An appraisal of the success of the two operations was made by consideration of both the patient's statement whether he was satisfied and the examiner's appraisal of that statement. In the sub-

stump. The third patient died of pneumonia after an emergency operation for bleeding gastric ulcer done in the presence of bilateral lobar pneumonia and portal hypertension. Although this patient is included in the calculation of the total mortality of 3.3 per cent after subtotal gastrectomy, such inclusion does not render this figure accurate for elective subtotal gastrectomy, which is 2 deaths in 89 cases, or 2.2 per cent. Although there were no postoperative deaths following vagotomy, there were 2 late deaths, 1 from periarteritis nodosa and the other from perforated recurrent ulcer.

Recurrent Ulcer

Among the 22 patients who underwent vagotomy 3 demonstrated peptic ulceration postoperatively: one, a persistent and reactivated duodenal ulcer, another, a recurrent duodenal ulcer after six months of relief, and a third, a fresh ulcer occurring in the stomach a few days after vagotomy for duodenal ulcer. Two of these patients showed absence of vagus function according to the generally accepted interpretation of the insulin test. In the third case an insulin test was not performed. One of these patients is now well after a gastric resection. Another had a thorough exploration of the esophagus from the root of the lung to the stomach to determine whether regenerated nerve fibers could be discovered. Although none could be found, he was again relieved for six months by the exploration alone but then returned with a perforated ulcer fourteen hours old and died rapidly in shock before suture could be done. Autopsy showed persistent

TABLE 8 Summary of Unfavorable Side Effects in 11 Patients Who Had Vagotomy in Addition to Gastrointestinal Anastomosis, as Compared with 11 Patients Who Received Vagotomy Alone

SIDE EFFECT	CASES OF VAGOTOMY WITHOUT GASTROENTEROSTOMY*	CASES OF VAGOTOMY WITH GASTROENTEROSTOMY†
Pain	4	2
Vomiting	8	1
Poor appetite	5	1
Diarrhea	3	1
Restricted diet	3	2
Dumping syndrome	0	4
Easy fatigue	2	3
Poor economic result	1	0

*The average weight gain in this group was 10 pounds and the average hemoglobin 90 per cent.
†The average weight gain in this group was 0 pounds and the average hemoglobin 85 per cent.

total gastrectomy group 41 (75.9 per cent) of the 54 patients were enthusiastically satisfied with the results of the operation. No patient was dissatisfied. In the vagotomy group 15 (68.1 per cent) of the 22 patients were enthusiastically satisfied, and 2 were dissatisfied. The examiner's appraisal in the gastrectomy group was that 28 (51.8 per cent) of the 54 patients had an optimal result, whereas only 4 had poor results. In the vagotomy group,

similarly, 10 (45 ± per cent) of the 22 patients had an optimal result whereas 4 had poor results. It is significant that the poor results occurred predominantly in the patients who had vagotomy alone rather than vagotomy in addition to a gastroenteric stoma (Table 8).

DISCUSSION

It is recognized that because of the manner of their selection the comparison between the two groups here presented is not strictly valid. Some of the contrasting results are explicable on the basis of differences in age, which might explain the difference in employment status and fatigability, for instance.

Another point in which the two groups differ is the fact that 31 ± per cent of the patients in the gastrectomy group, whereas none in the vagotomy group, had gastric ulcers. We have not, however, found the incidence of unfavorable side effects to be less in patients who have had subtotal gastrectomy for gastric ulcer than in those having subtotal gastrectomy for duodenal ulcer (Table 9).

Certain impressions can, however, be drawn from the study. Mortality following vagotomy has been slightly lower than that following gastrectomy. The causes of the deaths that have followed vagotomy, on the other hand, have often been unpredictable. This has not been true of the deaths following subtotal gastrectomy. The early recurrence of ulcer following vagotomy has not been strikingly less frequent than that following subtotal gastrectomy. The unfavorable side effects that follow vagotomy are as frequent as those following gastrectomy. They are, however, more likely to be gastrointestinal—that is, vomiting and diarrhea. In the gastrectomy group, dumping syndrome, failure to gain weight and loss of energy predominated. The patients who had a vagotomy with a gastroenteric stoma gained, on an average, no weight. It may be that the addition of such a stoma to the operation of vagotomy prevents symptoms of gastric retention but adds the factor of interference with nutrition that may plague the patient after gastrectomy.

In general the results in our small group and the impressions drawn therefrom have coincided with those of Allen.¹ We have found a slightly higher incidence of ulceration after vagotomy (3 cases in 22) than he reported (1 case in 75). Our good results in both the vagotomy and gastrectomy groups are about 10 per cent lower than his. For the purposes of the over-all impression, however, these differences are minor.

We recognize that a patient who enjoys a perfect result after vagotomy possesses a gastroduodenal tract that is anatomically and functionally more nearly normal than that of a patient who has received a subtotal gastrectomy. We hope that a larger experience with the procedure will teach

us how to make such results the rule. Until that occurs, however, it seems to us wise that as a routine policy subtotal gastrectomy should be the preferred elective operation for most patients with duodenal and gastric ulcers. Vagotomy we now reserve for the patient with marginal ulcer or the patient who is young and in whom a strong emotional background to the hypersecretion can be established either by laboratory test or by surmise from the patient's reaction to his environment. When

TABLE 9 Summary of Unfavorable Side Effects in 17 Patients Who Received Partial Gastrectomy for Gastric Ulcer Compared with 37 Patients Who Received Partial Gastrectomy for Duodenal Ulcer

SIDE EFFECT	GASTRIC ULCER*		DUODENAL ULCER†	
	NO OF PATIENTS	PERCENTAGE	NO OF PATIENTS	PERCENTAGE
Pain	2	11.7	1	2.7
Vomiting	3	17.6	6	16.2
Poor appetite	1	5.8	8	21.6
Diarrhea	1	5.8	3	8.1
Restricted diet	7	41.1	11	29.7
Dumping syndrome	10	58.8	15	40.5
Easy fatigue	9	52.9	12	32.4
Poor economic result	6	35.2	5	13.5

*The average weight gain in this group was 6.7 pounds and the average hemoglobin 80 per cent.

†The average weight gain in this group was 9 pounds and the average hemoglobin 78 per cent.

vagotomy is performed for duodenal ulcer a concomitant gastroenteric stoma is created to avoid excessive gastric retention.

SUMMARY

An analysis is made of a series of 120 definitive operations performed for peptic ulcerations of the stomach, duodenum and gastroenteric stoma with a view to comparing the results following subtotal gastrectomy and those following vagotomy.

The mortality was 3.3 per cent among 89 subtotal gastrectomies and 0 among 28 vagotomies.

Fifty-four patients who had subtotal gastrectomy and 22 patients who had vagotomy were examined four to twenty-four months after operation. There was 1 early recurrence of peptic ulceration in the former group, and 3 in the latter.

We have confirmed the findings of Allen that the incidence of unfavorable side effects was quantitatively comparable in the two groups and have concluded with him that for the time being the use of vagotomy should be restricted to patients with anastomotic ulcer and to young patients without pyloric stenosis and with a presumably strong emotional phase of gastric secretion.

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CLINICAL NOTE

DEVELOPMENT OF CARDIAC MURMURS IN SUCCESSFULLY TREATED CASES OF BACTERIAL ENDOCARDITIS

RICHARD T. BEEBE, M.D.,*

AND

JOHN K. MENEELY, JR., M.D.†

ALBANY, NEW YORK

THE presence of cardiac murmurs as an aid in the diagnosis of subacute bacterial endocarditis has been stressed in the past. Paul et al.¹ noted significant murmurs on admission in 100 per cent of their 44 cases treated with penicillin. Levine² states that "the absence of any murmur is a very reliable clue in eliminating the diagnosis of subacute endocarditis" and comments that he has seen only one case in which no murmurs were heard. White,³ however, mentions the development of murmurs during the course of the disease, and indicates that in rare cases no murmurs are ever present. The following cases, 2 of subacute bacterial endocarditis and 1 of acute bacterial endo-

carditis, are reported to emphasize two points: the necessity of suspecting subacute bacterial endocarditis in all patients with fever even if they have no previous rheumatic history and are without cardiac murmurs at the time of initial examination, and the necessity of considering healed bacterial endocarditis as a cause, per se, of persistent cardiac murmurs.

CASE REPORTS

CASE 1 (A. H. 161167). A 42-year-old man entered the hospital with the chief complaint of headache and fever for 3 weeks prior to admission. The onset of this illness had been ushered in by a shaking chill. The past and family histories were noncontributory, no history of rheumatic fever could be elicited.

Physical examination was entirely within normal limits. No splenic enlargement or petechiae were noted, and there were no heart murmurs.

The temperature was 100.6°F, the pulse 80, and the respirations 20. The blood pressure was 120/62.

Laboratory examination revealed a moderate anemia and a slight leukocytosis. A chest film was negative. The Widal and brucella agglutination tests were also negative.

On the day after admission, two small resolving hemorrhages were noted in the left optic fundus. Six days later, small hemorrhages were noted in the right fundus. Five days later, petechiae were noted in both the right and the left conjunctiva, and on the right abdominal wall. Numerous blood cultures were taken and reported as negative, but 1 month after admission three blood cultures drawn on the day of admission were reported as positive for *Streptococcus viridans*. The patient received a total of 35,000,000 units of penicillin intramuscularly over a 5-week period. The temperature fell slowly to normal and remained so for 23 days before penicillin was discontinued.

It was not until 6 weeks after admission that a blowing, Grade III systolic murmur was noted over the precordium, loudest at the apex and transmitted to the axilla.

*Professor of medicine Albany Medical College head Department of Medicine Albany Hospital.

†Assistant in medicine Albany Medical College medical director Albany Hospital.

The patient, as discharged, well and without complaints, 3 months after admission.

When the patient was seen for follow-up study, 9 months later, a forceful, Grade III systolic murmur was still noted over the entire precordium, associated with an absent mitral second sound. The heart border was enlarged to the left.

CASE 2 (A. H. A67506). A 60-year-old man was admitted to the hospital with the chief complaint of hematuria of 4 months' duration. 10 months before the onset of the hematuria a right-sided hemiplegia had suddenly developed and persisted. There had been a 30-pound weight loss over the 12-month period.

The family history was noncontributory, and the patient history of significance only in that the patient "thought he had a heart murmur" as a child.

Physical examination on entry revealed a mild right hemiplegia, but the remainder of the physical examination was entirely negative. No petechiae were noted. The spleen was not enlarged, and no heart murmurs were heard by a casual observer.

The temperature was 101.1, the pulse 90, and the respirations 30. The blood pressure was 134/82.

Laboratory examination revealed 5 to 8 red cells per high-power field in the sediment, a rather marked hypochromic anemia and a slightly elevated nonprotein nitrogen.

On the 5th hospital day, it was noted that the aortic second sound was accentuated, and it was thought that a very soft systolic murmur was heard in this area. Six days after admission, a small retinal hemorrhage was noted in the left eye. Three days later the spleen was found to be enlarged. Two weeks after admission the aortic systolic murmur had become very loud, fresh subconjunctival petechiae were noted, and 10 petechiae were discovered in the buccal mucous membrane. A blood culture on this day was positive for *Streptococcus*. Penicillin, in a dose of 1,000,000 units intramuscularly daily, was begun and continued for 3 weeks, with a rapid fall in temperature. Successive blood cultures were negative, and the patient was discharged approximately 6 weeks after admission still maintaining an elevated nonprotein nitrogen.

He was seen 6 months later with no significant change in renal condition, and with a Grade IV parasternal aortic systolic murmur and an aortic diastolic murmur.

CASE 3 (A. H. A43315). A 32-year-old man was admitted to the hospital with the chief complaint of spots on the legs. The spots had appeared 1 month prior to admission and had been associated with chills and fever. He had been studied by a physician, and the bleeding and clotting times were normal, one blood culture was negative. There had been an associated 24-pound weight loss.

The patient history revealed that the patient had had rheumatic fever as a child, but no murmur had ever been noted by his family physician. One year before admission the patient had been discharged from the hospital, and no murmur had been noted at that time, although specifically sought for in view of the past history of rheumatic fever. Eight months prior to the present illness, the patient had been hospitalized for hemorrhaphy, and at that time no murmur had been heard on examination of the heart.

Physical examination revealed a generalized alopecia, color to the skin and purpuric eruptions over the lower extremities. The spleen was palpable. The heart sound were described as being forceful. Two examiners noted no murmurs in the heart, whereas a third believed that there might be a very soft apical presystolic murmur.

The temperature was 100.4°F, the pulse 94, and the respirations 24. The blood pressure was 130/50.

Laboratory studies revealed a moderate leukocytosis and anemia. X-ray films revealed a mitral configuration of the heart. Blood cultures drawn on the first 4 days of the hospital stay were positive for hemolytic streptococcus.

Intramuscular administration of penicillin was begun at this time and continued for 4 weeks. A total dose of 21,000,000 units was given. The temperature fell to normal after the 1st day of this therapy and remained so throughout the remainder of the hospital course. During the hospital stay, a very loud, apical, systolic and presystolic murmur developed, with a diastolic murmur at the aortic area.

The patient was discharged after 6 weeks in the hospital, symptom free. He has been followed for a year and a half in the outpatient department, and at the present time he has Grade IV aortic and mitral systolic and diastolic murmurs.

SUMMARY

Three cases are reported in which permanent cardiac murmurs had their initial appearance during the course of bacterial endocarditis, successfully treated with penicillin. It is suggested that the absence of cardiac murmurs need not militate against the initial diagnosis of subacute bacterial endocarditis.

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Correction. In the article entitled "Aureomycin in the Treatment of Primary Atypical Pneumonia," by Finland, Collins and Wells, which appeared in the February, 1958 issue of the *Journal*, the first sentence in the third paragraph on page 246 should be changed to read: "The patients with whom we are concerned in the present evaluation were acutely ill and febrile when aureomycin was started. In each the history and the physical, x-ray, and laboratory findings were all characteristic of primary atypical pneumonia."

MEDICAL PROGRESS

SYPHILIS*

G MARSHALL CRAWFORD, M D †

BROOKLINE, MASSACHUSETTS

THE preponderance of publications regarding syphilis continue to emphasize penicillin. A major impediment to penicillin therapy was its requirement of hospitalization. Subsequent development of repository types of penicillin products that require but one injection per twenty-four hours has practically eliminated the hospitalization factor. Continued improvement of these products and their wider application have proved successful. The time factor remains essentially the same whether rapidly utilized penicillins or slowly absorbed preparations are employed. Thus, a large majority of patients can be treated on an ambulatory basis, permitting more efficient utilization of clinic personnel, both professional and clerical. The ten-day treatment schedules that have been widely employed are resulting in a high percentage of patients completing their therapy in contrast to the frequent lapses and defections that accompanied traditional chemotherapy. The percentage of reactions is apparently no greater with repository penicillin products than with the rapidly absorbed types. Mentally incompetent patients are an obvious exception to ambulatory treatment and must, of course, be incarcerated. Cardiovascular syphilis and visceral lesions in which a Herxheimer reaction would be disastrous seem to be the only outstanding contraindications to treatment with penicillin in oil.

PUBLIC HEALTH

During the past ten years a nationwide campaign for the control of venereal disease has been in progress, headed by the United States Public Health Service. Remarkable strides have been made in all respects, and a gradual reduction of the incidence of all venereal diseases has been attained. The armed forces of the United States passed through World War II with the lowest venereal-disease rate of any nation in any major war. A rise in the civilian rates was feared in the postwar period, but control measures have been maintained with such efficiency that no appreciable increase has been recorded. Current methods of therapy are remarkably more efficient than ever before, but physicians cannot treat the disease until infected persons are at hand. Finding the infectious

patients and bringing their disease under control before it has been spread is the primary objective. Continued public interest and support is essential. There are three main points of primary importance: public education and information, mass blood testing examinations and contact tracing. Diligent pursuit of these case-finding activities will constitute the essence of future progress in the control of venereal disease.

Control Measures

Evidence that the aforementioned control measures are not being neglected in the postwar period is seen in publications from the Venereal Disease Division of the United States Public Health Service.^{1, 2} In a ten-year period the number of deaths due to all forms of syphilis has been reduced by a third, and the infant deaths by two thirds. This notable accomplishment is largely attributable to the nine basic principles of public-health control of syphilis. These include the development of a trained public-health staff, case-finding and case-holding technic, laws requiring premarital and prenatal serodiagnostic tests, the expansion of diagnostic services, the provision of public treatment facilities, the distribution of anti-syphilitic drugs by state health departments, emphasis on routine serodiagnostic tests, a program of scientific information directed to health officers and practicing physicians and a vast public-education campaign. One of the major accomplishments has been the transference of the word syphilis from the unmentionable category to everyday usage among the public. It is estimated that of all patients treated today for primary and secondary syphilis, two thirds voluntarily seek diagnosis as a result of public education among civilians and the information disseminated among the armed forces. Under the direction of the Public Health Service, extensive investigations into a wide variety of fundamental research problems have been under way for years. Greater emphasis will be placed on this work as one of the more important future potentialities. Thirty-five per cent of all cases of syphilis reported each year have been found by private physicians in the regular course of their daily practice. A still larger percentage is probably under treatment in the hands of the private physician, and authorities are in full cognizance of these facts. More assistance will be extended to the practicing

*From the Department of Dermatology and Syphilology, Harvard Medical School and the Massachusetts General Hospital.

†Instructor in dermatology Harvard Medical School dermatologist Massachusetts General Hospital.

physician in the management of his cases and in case-finding activities

The Venereal Disease Division of the United States Public Health Service is implementing case-finding activities throughout the country by the preparation of fifteen-minute radio programs to be released through district offices for use by state and community health departments.³ These transcriptions will deliberately de-emphasize technical information, rather, they will stress when to suspect infection and where to go for treatment. The accent is on hope rather than fear. Various transcriptions are in preparation with special appeal to particular audiences such as sports fans, mystery-story fans, soap-opera fans and hillbilly-music followers. The scripts have been prepared by some of America's best radio writers, and the programs will feature well known performers. These transcriptions should have been released some time before the publication of this review.

The Chicago Health Department has made extensive use of telegrams in case-finding and case-holding at its intensive treatment center.⁴ Of 1541 contacts to whom telegrams were sent, 47.0 per cent reported to the health department within three days. A total of 225 patients, or 1 out of every 7 persons to whom telegrams were sent, were placed under treatment for primary or secondary syphilis. The telegram technic proved relatively inexpensive and was unobjectionable to the persons involved. It was not only effective but also time-saving.

Intensified campaigns to bring to light as much syphilis as possible have been carried out in many communities through the country. Almost uniform success is evident in numerous publications from all quarters. Particularly outstanding are the accomplishments in the State of Georgia.⁵ Here is an excellent illustration of what can be attained via the mass blood-testing technic, which was carried out in eight large communities between October, 1945, and August, 1947. Approximately 288,000 persons were tested, and a total of 9042 previously unknown cases of syphilis were discovered. During the special program, ten to forty-seven times as many new cases of syphilis were discovered as would ordinarily have been reported during an equal period. It was found that a large proportion of the population of a community will seek a blood test in response to an intensive publicity campaign, without the backing of a law. Intensive contact investigation conducted jointly with the mass blood testing led to the discovery of still more primary and secondary disease. These achievements set a remarkable example for most other states.

Mortality

Statisticians of the United States Public Health Service have prepared an analysis of the mortality

from syphilis for the years 1933-1945.⁶ The analysis begins with 1933 because that was the first year in which the entire United States was included in the vital-statistics registration area. Perhaps the most outstanding trend in this survey is the decrease in the total death rate from syphilis beginning with 1937 and continuing into 1946, the rate decreasing by approximately 25 per cent in that time. Syphilis remains a major cause of death, however, particularly in the Negro population—only eight conditions exceeded syphilis as a reported cause of death for Negroes in 1945. Improvement in therapy and treatment facilities has been an important factor. Intercurrent diseases that may cause death can also alter statistics. The difficulty of diagnosing syphilis as the cause of death may enter into the problem. The willingness of physicians to report syphilis as the cause of death when they have made the diagnosis may be influenced toward concealment because of social taboos or insurance policies that exclude syphilis as a mortality risk. All these factors are more or less constant, however, and should serve only to reduce the over-all quantity of reported cases. It is considered by the Public Health Service that the reporting by physicians has actually improved. The trend of infant deaths from syphilis per 1000 live births has been in the same direction as the general mortality trend, although the rate of decrease has been greater in the infant group, dropping from 0.79 to 0.25 during the thirteen-year period of analysis.

Statistical Trend

In 1948 there were indications in various publications that the syphilis rate in the United States had increased alarmingly since the end of the war. Statistics from the United States Public Health Service contradict these claims.⁷ Statements were presumably based on the number of cases of early syphilis reported among civilians rather than on rates calculated for the whole population of the United States. The tables do indicate a moderate increase of early syphilis among civilians in 1946 and 1947, but this was undoubtedly due to the return to civilian life of millions of young adult men in the age group in which new syphilis infections frequently occur. At the same time there has been a steady decrease in the rates of congenital and late syphilis, and the total syphilis reported has shown a continuous decline from 1933. When the total of civilian and armed forces is considered, the early infections actually showed a decrease in 1947 as compared to the year before. A survey of the reasons for reporting to venereal-disease clinics indicates that 64.2 per cent of patients came of their own initiative.⁸ This was a widely scattered study covering several districts in each of seventeen states. Such a large percentage of voluntary clinic attendance portends the value of public education regarding venereal disease. The same analysis

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G MARSHALL CRAWFORD, M D †

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*From the Department of Dermatology and Syphilology, Harvard Medical School, and the Massachusetts General Hospital.

†Instructor in dermatology, Harvard Medical School; dermatologist, Massachusetts General Hospital.

obviously the most potent preparation, and penicillin K the least potent, whereas F and X hold intermediate positions between these extremes. Crude sodium penicillin is probably more effective than F, X or K. Bacitracin is also relatively inefficient.¹⁶

Methods of Administration

The optimum time-dose relation in the administration of penicillin for the treatment of syphilis is yet to be established. At least three variables may modify therapeutic efficiency: the number of injections, their frequency and the total amount of penicillin administered. It has been shown in experimental rabbit syphilis that the greater the number of injections, the less the total amount of penicillin required for cure.¹⁹ Lengthening the duration of treatment has a similar effect on the curative dose. When injections were given so frequently as to produce cumulative effects on the penicillin blood level, therapeutic efficacy was paradoxically reduced. Although the therapeutic action of penicillin clearly involves both the tissue concentration and the time over which it acts, the latter time factor is by far the most important. Low concentrations acting over a long period are more effective than high concentrations for a short period. Thus the interval between injections is not so important, provided they are not given too often. The use of any procedure that delays the absorption and excretion of penicillin should have the same effect as increasing the frequency and number of injections.

In a comparison of subcutaneous versus intramuscular administration of penicillin, there were no significant differences in the plasma penicillin levels.²⁰ Three purified preparations, the amorphous, and crystalline sodium penicillin and crystalline potassium penicillin, gave essentially the same results. It has been demonstrated that penicillin is readily absorbed through the vaginal mucosa and appears in the blood in high therapeutic levels.²¹ Ten patients were used, and although there were wide individual variations, probably owing to loss of penicillin from the introitus, therapeutic levels were maintained up to three hours in all cases. Rabbit syphilis can be controlled by oral administration of penicillin, but the curative dose is excessive.²² This approach is not advisable in the human disease.

There is further confirmatory evidence of the value of penicillin oil in the treatment of rabbit syphilis.^{23, 24}

Prolonged Penicillin Action

Earlier products with penicillin in oil and beeswax had the disadvantage of being solid at room temperature and therefore difficult to administer. Liquid preparations of penicillin in oils that are fluid at room temperature and comparable in com-

position with the original products are now available commercially. The duration of the penicillin blood levels following the intramuscular injection of these "liquid" preparations has been studied and found satisfactory.²⁵ A procaine salt of penicillin G suspended in sesame oil has been employed at the Mayo Clinic and elsewhere with approval.²⁶⁻²⁸ The maximum serum penicillin concentrations obtained with procaine penicillin G in oil were lower than those after a similar dose of the oil and beeswax product but showed considerably more uniformity throughout the twenty-four hours following injection. A still further improvement in these repository types of penicillin products is claimed with the introduction of the principle of suspending penicillin salts in peanut oil, jelled with 2 per cent aluminum monostearate.²⁹ Several salts of penicillin were tested in this vehicle, and the absorption was delayed longer than when the same salts were suspended in peanut oil alone or in peanut oil and wax. Aside from the occasional allergic reaction to penicillin, there was no case of undue irritation or untoward effects, although the series of patients treated was small.

A possible further fruitful avenue is the study of insoluble metallic and organic salts of penicillin.^{30, 31} Insoluble salts with heavy metals have not been extensively used because such metallic ions inactivate penicillin. It was found however that insoluble metallic and organic salts of penicillin were apparently reactivated *in vivo* and produced quite respectable penicillin blood levels in rabbits as long as twenty hours later. This work bears further study.

Continued investigation of the effect of caronamide for its value in prolonging the effective therapeutic levels of penicillin has been encouraging. In experimental pneumococcal and typhoid infections in mice it is apparent that a therapeutic effect may be obtained with much smaller doses of penicillin when caronamide is administered concomitantly, and that higher and more prolonged penicillin levels are obtainable with caronamide than with similar doses of the antibiotic administered alone.³² It has been demonstrated that caronamide has no intrinsic bacteriostatic activity and it does not increase the *in vitro* bacteriostatic effect of penicillin so that the intensified *in vivo* effect of penicillin in the presence of caronamide should be due to enhanced and prolonged penicillin plasma levels. This suggests that infections caused by organisms relatively resistant to penicillin might be within the limits of practical penicillin therapy if caronamide were used. The effect of the latter drug has been found to be greater in older persons.³³ The only toxic effects noted have been nausea and mild diarrhea in a few cases. Caronamide can be used orally in conjunction with the oral administration of penicillin but is much more effective when the latter is given by intramuscular injection. Its

pointed out that almost 25 per cent of the patients with previously untreated primary or secondary syphilis came to the clinic as a result of contact investigation. Such an appreciable figure illustrates what can be accomplished by efficient case-finding and contact-tracing measures. The remaining small percentage came for other reasons such as prenatal or premarital blood testing, health-card applications and police or court orders, and because of blood examination for selective service or on separation from the armed forces.

EXPERIMENTAL STUDIES

It has been known for some time that processed blood stored in banks does not transmit syphilis regardless of infection in donors. New confirmation of this fact is in evidence from animal experimentation.⁹ Rabbits inoculated with stored dried material failed to develop evidence of syphilitic infection during three successive subtransfers observed for as long as thirteen months. It was obvious that *Treponema pallidum* suspended in saline-blood serum becomes avirulent and is apparently killed during the freezing and drying procedures. The danger of transfusion syphilis obviously seems to be eliminated with the use of processed human plasma or blood.

Immunity

It is accepted that at least some degree of true immunity develops during the course of syphilitic infection. Numerous efforts to produce this immunity by artificial means have been uniformly unsuccessful. A new attempt by the repeated subcutaneous injection of lyophilized spirochetes alone and with adjuvants failed to protect rabbits against minimal infectious inoculums of *T. pallidum*.¹⁰ It was observed that the injection of these antigens did produce positive serologic tests for syphilis in the same animals, this response should at least indicate a reaction in the host and provide some encouragement for investigators in that field. The relative cross immunity among three varieties of treponemes has also been investigated in rabbits.¹¹ Syphilis, yaws and venereal spirochetosis of rabbits were each found to generate some degree of immunity against treponemes causing the other infections concerned, as compared to control groups. The inoculations used probably contained many times the minimal infective dose of the various organisms, which subjected the acquired resistance of the animals to an unusually severe test. The definitely greater resistance to *T. pallidum* certainly indicates further study of the potentialities of other treponemes as immunizing agents. Methods of counting spirochetes have made possible the determination of the minimal infectious inoculant, which has proved to be one spirochete.¹² One or two spirochetes were regularly infectious to rabbits. There was no appreciable effect on incubation

period until as many as 10,000 organisms were injected. An inoculum of 200,000 organisms brought about another distinct decrease in incubation period. A rigid control of the size of the inoculant is obviously necessary for experimental studies on chemoprophylaxis, abortion or treatment of syphilitic infection. This same work with skin inoculation experiments enabled an estimation of the average rate of multiplication of the spirochetes in vivo to be thirty hours for each division of one spirochete into two spirochetes. Further study, with the application of this information to rabbit syphilis, revealed that progressively larger doses of penicillin were necessary to protect the animals as the size of the inoculum was increased.¹³ In another phase of the work, when a fixed intratesticular inoculation was used, the amount of penicillin necessary to prevent infection remained at a constant level for four days. By the end of the second week more than seven times this dosage was needed to prevent infection, and by the end of the sixth week, after a chancre had appeared, more than thirty times the amount was required. This leads to speculation regarding the possibility of aborting syphilis in man by small doses of penicillin administered during the incubation period. If rabbit syphilis and human syphilis are comparable, and assuming that penicillin behaves similarly in both, comparatively small amounts of penicillin might be hopeful abortive therapy in some early infection if given as soon as four days after exposure.

Further evidence that immune factors do occur in rabbit syphilis is now available.¹⁴ A sizable group of animals was inoculated with syphilis, observed for eight months, given a known curative dose of penicillin and, ten days later, reinoculated. Only 53 per cent were found to be reinfected, and theirs was a symptomless invasion, the syphilis having been proved by transfer of lymph nodes to normal animals for proof of the infection. When the same procedures had been carried out in early syphilis of rabbits, 73 per cent presented a symptomless reinfection. It is obvious therefore that the immune factors occurring in early latent syphilis are more forceful than those observed in early infectious syphilis. The potency of the protective reaction varied with the duration of the disease.

Species of Penicillin

A co-operative investigation of the efficacy of several species of penicillin in the treatment of experimental syphilis corroborates earlier knowledge that penicillin G is by far the most effective specimen.¹⁵ Penicillin F required about six times as large a dose as penicillin G to achieve the same effect. Penicillin K was distinctly inefficient, and the data on penicillin X were so discrepant as to be insufficient for comparison. Further independent studies are corroborative.¹⁶⁻¹⁸ Penicillin G is

SEROLOGIC PROBLEMS

Cardiolipin

In the last few years cardiolipin has been employed as a new phospholipid content of antigens for serologic tests for syphilis. It was hoped that this new substance would be the answer to simplification or clarification of the serology of syphilis. So far cardiolipin has not fulfilled either role. There have been improvements, but even more technics seem to have appeared and simplification is far from achieved. The clinician who interprets the results of laboratory procedures for his patient still cannot shift any responsibility from his own shoulders to that of the laboratory technics or the personnel performing them.

The Venereal Disease Research Laboratory slide flocculation test for syphilis was one of the first to employ the cardiolipin antigen and has been studied most extensively.^{44, 45} More than 8000 serums from syphilitic donors taken before, during and after treatment have been examined by this technic. An analysis of results with comparative tests indicates that the slide test functions at a satisfactory level of sensitivity, produces a relatively low proportion of weakly positive reactions and yields satisfactory specificity on specimens from nonsyphilitic persons. In the laboratories of the New York City Department of Health this test was compared with the Mazzini and Kahn flocculation tests and the Kolmer complement-fixation test in 57,372 routine specimens.⁴⁶ The sensitivity of the four tests, in order of reactivity, was the Mazzini slide test, the Venereal Disease Research Laboratory slide test, the Kolmer complement-fixation test and the standard Kahn test. The reliability of the Mazzini and the Venereal Disease Research Laboratory procedures as screening tests was attested by their agreement in the negative reaction in all but 0.8 per cent.

Hinton⁴⁷ has tested about 1000 carefully selected specimens by his technic with an antigen prepared from cardiolipin and lecithin. Results appear to be just as specific, but considerably more sensitive than those obtained with the Hinton test when the indicator was prepared from an extract of beef heart. Kahn has studied the effect of various lipids on his serologic tests and reports that lecithin can be used to correct oversensitive antigens since it reduces their reactivity.⁴⁸ On the other hand cephalin was found to increase the sensitivity of undersensitive antigens to bring them up to the requirement of the standard Kahn antigen.

A comparison of the cardiolipin and Kline antigens appears in a report of clinic and serologic evaluation of 27,103 consecutive slide tests for syphilis with optimum cardiolipin-lecithin antigen and Kline antigen.⁴⁹ The cardiolipin slide test gave results of decidedly greater specificity and much greater sensitivity than diagnostic Kline antigen

emulsion and was also distinctly more specific in nonsyphilitic serums than the Kline exclusion antigen emulsion. Kline⁵⁰ himself advocates the use of a single standard test employing the cardiolipin antigen. He believes that the flocculation reaction is better suited for use in the standard test for syphilis than in the complement-fixation reaction, which requires more ingredients and more time. He further believes that the slide technic offers more advantages for a standard test than the tube flocculation technic. The application of cardiolipin antigen to the Kline procedure is reported from another laboratory, with highly satisfactory results in a large series of cases.⁵¹ The test showed a significantly higher sensitivity than either the standard Kahn or the Kolmer test, and the specificity was essentially the same as that shown by the Kahn reaction. In the special instance of malaria the specificity of the cardiolipin test was outstanding.

The cardiolipin antigen has also been successfully adapted for use in the Kolmer complement-fixation test for syphilis.⁵² Cardiolipin antigen was found slightly more sensitive than the standard Kolmer technic in testing known syphilitic serums. Specificity was essentially the same with the two procedures in testing known nonsyphilitic persons. Specimens from patients with active yaws showed the same relative reactivity in the two tests.

Quantitative Tests

Quantitative determinations can be made by means of both flocculation and complement-fixation technics through a series of dilutions. Their employment is indicated in conjunction with intensive antisyphilitic treatment for appraisal of the various methods during treatment and in follow-up study of the early syphilis so treated. Further value lies in detecting serologic relapse before clinical evidence appears, in darkfield-negative primary syphilis (in which a low but increasing titer may be of great significance) and with suspected congenital syphilis in the newborn. Quantitative tests also have certain value in attempts to decipher a possible false-positive reaction, especially since none of the verification tests so far developed have been completely satisfactory.

A rapid slide flocculation test for the titration of antibodies in syphilitic serum has been described.⁵³ The data presented indicate that this test may be satisfactorily substituted for the conventional tube dilution procedure using either the cardiolipin or Mazzini antigens. An application of the Kahn "optimal zone reaction" has been described for use in seronegative cases of neurosyphilis.⁵⁴ This technic is more specialized than the usual quantitative reactions but may be worth while in some of the puzzling infections of the central nervous system in which other serologic reactions are consistently negative. Most reviews of the various tests and

effect is less constant when it is used in conjunction with the injection of penicillin in oil. Sodium benzoate has been found as effective as caronamide in increasing plasma penicillin concentrations.³⁴ The ingestion of both sodium benzoate and caronamide by subjects receiving penicillin by mouth resulted in a greater enhancement of plasma penicillin concentration than that achieved by either of these agents alone. Although caronamide has not yet been widely used, it is thought to be free of renal, bone-marrow or hepatic effects, and has not yet been observed to produce dermatitis or drug fever.³⁵ Caronamide is administered by mouth, usually in doses of 2.0 gm. every three or four hours, concomitantly with penicillin. Its effect as a renal "retardant" begins to wear off after two hours.

In a dissertation on the significance of penicillin blood levels, Eagle³⁶ points out that concentration of penicillin in the blood has significance only in that it "provides a rough measure of the concentration at the foci of infection in the tissues." Thus, the therapeutic effect of a given dosage of penicillin depends on the total length of time the concentration of penicillin in the blood is at maximal bactericidal levels. The danger is greater with organisms that recover rapidly from penicillin action or multiply at a fast rate than with organisms that multiply only slowly, such as *T. pallidum*. It is obvious that the plasma level of penicillin should not be allowed to drop below the concentration that, in vivo, is sufficient to kill the organism in question faster than the organism can multiply. Another communication presents tables and graphs that enable the physician to determine the frequency at which a given dose should be injected and the dosage of penicillin that should be used at stated intervals to maintain given concentrations of penicillin in the plasma.³⁷

Other Therapy

Bismuth has been widely employed as an adjunct in the penicillin treatment of syphilis, but there has been little direct experimental evidence supporting such use. It is known that mapharsen and penicillin are synergistic in experimental syphilis, and by analogy it has been assumed that bismuth might similarly aid the spirocheticidal action of penicillin. A study of experimental rabbit syphilis has been confirmatory.³⁸ Bismuth and penicillin were shown to be as synergistic as mapharsen and penicillin, and bismuth should apparently be as effective as mapharsen in this combination. Maximum synergism was obtained when bismuth and penicillin acted simultaneously through the use of a water-soluble bismuth preparation. This is because of the delayed absorption of bismuth salicylate, which, however, also reduced the curative dose of penicillin whether given during or after the penicillin treatment. Bismuth did not affect

the penicillin blood level. Since bismuth is so relatively innocuous as compared to mapharsen, it should obviously replace the latter for combined therapy with penicillin.

A bismuth salt suitable for oral administration has been shown to produce therapeutic levels and is on the whole well tolerated.³⁹ Relatively few patients with early syphilis have been treated with this agent, responses were typical of systemic bismuth therapy. Bismuth by mouth is certainly not to be recommended for the treatment of syphilis in any stage unless more effective measures are contraindicated. Nevertheless, it might prove with further study to be useful as an adjuvant therapy in conjunction with penicillin.

The value of fever therapy alone or in conjunction with other methods has long been appreciated in the treatment of late syphilis, especially neurosyphilis. Recent studies have been undertaken to determine the possible application of this modality to early syphilis. It has proved useful, though more hazardous than other approaches, and reports are still appearing to that effect.⁴⁰ Penicillin therapy has almost entirely superseded such drastic forms of treatment, but they may be kept in mind for infrequent resistant cases.

A post-mortem study of the aortas of 45 patients with syphilitic aortitis bears out the long-established tenet that even traditional chemotherapy exerts a profound influence on the inflammatory process in the aorta.⁴¹ Nineteen of these patients had received the so-called minimal standard therapy of approximately 20 arsenical and 20 bismuth injections, and only 3 of them exhibited active inflammation in the aortic walls. Progressively greater activity was observed as the amount of treatment decreased. There was apparently no correlation between the duration of infection and the activity of the aortitis. The isolation of virulent *T. pallidum* from the aorta thirty-two hours after death is most interesting, since the demonstration of viable treponemes is generally considered difficult in late lesions.⁴² Aortic tissue was inoculated into a rabbit thirty-two hours after the death of the patient in this case. Viable organisms were also isolated from juxta-articular nodules. The patient had had syphilis for twenty-five years and had received no therapy. This event is obviously of practical importance to pathologists from the standpoint of possible accidental infection during post-mortem examinations. Motile spirochetes have been found in human autopsy material refrigerated for as long as forty-eight hours.⁴³ In fresh material from infectious lesions, viable treponemes can be maintained in an incubator of 37°C for as long as fourteen days. The enormous numbers of *T. pallidum* that may be found in macerated fetuses suggest the possibility that this organism can multiply in dead tissue under anaerobic conditions.

all publications show a failure rate of 10 per cent or higher, which is too large for complacency.

Numerous words of caution have been uttered regarding the danger of masking early syphilis with the penicillin treatment of gonorrhea. This has been excellent advice. There is one report available of 19 cases of early syphilis observed to develop after 150,000 units of penicillin for gonorrhea.⁶³ The appearance of syphilis was not delayed longer than three months in any case. These observations should actually serve as another word of warning, since the amount commonly given for gonorrhea is 300,000 units of penicillin. One could reasonably expect that this dose would delay the appearance of early syphilis for a decidedly longer time. A follow-up period of not less than six months seems only reasonable for penicillin-treated gonorrhea patients.

Syphilitic Chancres

In a survey of 680 male patients with early syphilis one observer found the primary lesion on the glans penis in approximately half the cases.⁶⁴ Twenty-five per cent of the chancres were on the prepuce, 15 per cent were on the penile shaft, and 10 per cent were paragenital or extragenital. An interesting observation in that series was the fact that chancres on the shaft of the penis were seldom indurated. There were multiple chancres in only 12 per cent of the patients observed. In another series of similar size, the surprisingly higher figure of approximately 40 per cent multiple chancres was found.⁶⁵ The incidence of multiple lesions was consistent in both sexes. If multiple chancres actually occur as often as this figure indicates, older teachings must be revised. These reports should stimulate the physician to be more on the alert for multiple chancres that might otherwise mislead him to the extent of mistaken diagnosis or perhaps undue delay in establishing a correct appraisal of primary syphilis.

Extragenital chancres are a still more likely possible cause of incorrect or unduly delayed diagnosis. A low index of suspicion of the primary lesion of syphilis is bound to interfere with its recognition when the location is extragenital. Early diagnosis is of greatest value in primary syphilis, not only from the standpoint of the patient, whose chance for a true biologic cure diminishes with time but also from the view point of transmission of the disease to others. A study of 219 patients with extragenital chancres has been published from the Johns Hopkins Hospital.⁶⁶ A significant preponderance of extragenital lesions occurred in the female patients and in the white race. In the majority immediate sexual contact with infectious lesions of syphilis seemed the most likely explanation. Except in children, by far the largest number of extragenital chancres occurred in or adjacent to the buccal cavity. Multiple extragenital initial lesions occurred in only 9.4 per cent of the patients.

A surprising frequency and variety of erroneous diagnoses were found in the records. Any indolent indurated lesion anywhere on the body, especially if accompanied by unilateral adenopathy, should warrant the suspicion of syphilis. The diagnosis rests on the use of the darkfield microscope and serologic tests for syphilis.

Penicillin Therapy

Treatment schedules in use during the early history of penicillin often employed dosage plans that proved to be too small. An illustration is a series of over 400 cases of early syphilis treated with 1,200,000 units over a period of three and three-fourths days.⁶⁷ Twenty per cent of this group were found to be treatment failures at the end of fifteen months' observation. Rapid penicillin treatment, employing massive doses intravenously, has also proved unsatisfactory.⁶⁸ A group of 129 patients received 10,000,000 units of penicillin intravenously in a twenty-four-hour period, but the treatment failed in approximately half the group. Another series of 275 patients with early syphilis were given from 10,000,000 to 25,000,000 units by the continuous intravenous drip method over a period of twenty-four hours.⁶⁹ Even with the maximum dosage 35.2 per cent were failures, indicating an obviously ineffective treatment schedule. Reactions to therapy were frequent but generally mild, and all patients having reactions recovered rapidly. The obvious inadequacy of these attempts at rapid massive penicillin therapy is a perfect example of the importance of the time factor in treatment. Almost all studies of penicillin treatment have indicated that shortening the elapsed time of therapy cannot be counterbalanced by increasing dosage.

An analysis of 22 different treatment schedules employing penicillin for previously untreated secondary syphilis, utilizing at least 50 patients for each, has been published by the United States Public Health Service.⁷⁰ In some plans penicillin was used alone, and in others various adjuvants were employed. The optimum therapy schedule appeared to be 3,400,000 units of penicillin in aqueous solution given in injections of 40,000 units each at two-hour intervals (seven days). Results were tabulated at twelve to fifteen months after therapy. Treatment and follow-up data were furnished by fifty state and locally sponsored rapid-treatment centers. Poorest results were obtained with schedules in which the total amount of penicillin was given in thirty hours or less regardless of dosage or adjuvant therapy. A subsequent report from the same source summarizes the principal facts of clinical importance in all phases of syphilis.⁷¹ It is pointed out that up to the end of 1947, at least 500,000 patients with syphilis in various stages had been treated with this antibiotic, the agent most employed in syphilotherapy in the United

their respective significance or special points of application point out the complexity of the problem.⁵⁵ Harris⁵⁶ has described a simplified reporting method that may be applied to all flocculation and complement-fixation tests for syphilis that employ serum and spinal-fluid dilutions. Quantitative reporting is not similar for the many different tests for syphilis, even in cases in which a common term such as "units" is used. The units of one testing procedure may have no constant relation to the units of another. The differences in reported titers are attributable to the dissimilar methods of calculation and interpretation applied to observed findings. It is suggested that quantitative serologic reactions be reported in terms of the greatest dilution in which the tested specimen produces a positive reaction. By this means, reactions of identical intensity would receive the same report in terms of dilutions, even when different testing methods are employed. This method of reporting can be incorporated into a testing routine without modification of existing test mechanics, and the reactivity levels would not be affected. Such simplified reporting would remove much of the unwarranted burden of confusion in cross interpretation that is placed upon the clinician.

False-Positive Reactions

No outstanding advance has as yet been reported toward the solution of the dilemma of false-positive serologic tests for syphilis. Kolmer⁵⁷ says that no test can be sufficiently sensitive for the detection of all cases of syphilis. He points out that any method now in use can be made more sensitive by technical modifications but only at the expense of increased falsely positive reactions. It is obviously far better to miss the serum diagnosis of an occasional case of chronic syphilis than to incur the risk of false-positive reactions in nonsyphilitic persons. Accurate clinical judgment should not be overruled by negative reactions, but at the same time positive serologic reports cannot be ignored simply because they seem to be the only evidence of disease. False-positive reactions may be suspected when they are consistently weak or doubtful with occasional strong positive reactions. Discrepancies in serologic reports from different laboratories should be suspected. A third clue is consistently negative complement-fixation reactions in the face of positive flocculation tests. In any of these circumstances a diagnosis should probably be withheld, with repetition of testing procedures at regular intervals over a period that may extend as long as six months.

In recent years smallpox vaccination has been repeatedly maligned as a cause of false-positive reactions in serologic tests for syphilis. The limited variola epidemic in New York City in 1947 gave rise to a city-wide vaccination program and provided an excellent opportunity for the study

of possible false-positive reactions for syphilis. Over six million persons were vaccinated, but no increase was noted in the percentage of serologic reactors during the period following the mass vaccination program.⁵⁸ All routine blood specimens forwarded to the New York Bureau of Laboratories are screened by the Mazzini slide test, and positive or doubtful serums are confirmed by the standard Kahn and Kolmer tests. Vaccinations against smallpox may occasionally produce a false-positive serologic test for syphilis, but it need seldom be confused with true syphilitic reactions if tests are employed during a period of observation extending over several weeks. Perhaps undue emphasis has been placed on this possible cause of serologic confusion. Although not primarily under suspicion, penicillin therapy has been ruled out experimentally as a source of false-positive reactions for syphilis.⁵⁹

In one survey of the enigma of serodiagnosis in syphilis, it is pointed out that high specificity rather than high sensitivity should be the primary aim of the serologic test.⁶⁰ Three main reasons for the occurrence of false-positive tests are emphasized: technical errors, presence of reagent in the blood of normal persons and affliction with a nonsyphilitic disease that produces a positive reaction. It is pointed out that the various stages of syphilis react differently to the serologic tests and that they are least dependable in untreated latent syphilis, in which results are variable. It should be stressed that even the most competent syphilologist with extensive laboratory facilities at his disposal will frequently be confronted with serodiagnostic problems that are incapable of solution without prolonged periods of repeated testing and that the ultimate decision often cannot be reached on the basis of laboratory findings alone. A thorough history and careful complete physical examination are required before the combination of clinical judgment and serologic reports can be correctly analyzed.

Complement-fixation tests are occasionally impeded by anticomplementary serum. A procedure has been outlined that seems to permit the satisfactory performance of a Wassermann test on such anticomplementary serums.⁶¹ A colored slide flocculation test for the diagnosis of syphilis has been described.⁶²

EARLY SYPHILIS

Penicillin has been used more extensively in the therapy of early syphilis than in any other phase of the disease. Although this form of treatment has been eminently successful, the multiplicity of therapy programs that are being tried and the variation in schedules that have been recommended are proof that selection of the ideal penicillin regimen for early syphilis is still far off. Most plans of treatment require 2,500,000 units or more of penicillin in not less than seven or eight days, many advocate far higher dosage and longer time schedules. Almost

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States today It was stated that penicillin in oil and wax constituted the only practical method in the treatment of syphilis and provided proved effective blood levels of at least three to five times the duration afforded by aqueous penicillin in comparable amounts The recommended dosage for early syphilis in that report consisted of 4,800,000 units, with intramuscular doses every two or three hours for a period of seven and a half days The schedule advised for ambulatory treatment with crystalline penicillin in oil and wax consisted of the intramuscular administration of 6,000,000 units in ten injections over a period of ten days Adjuvant therapy with arsenic, bismuth or fever was advised as a combined therapeutic attack in patients who failed on an original course of penicillin alone A chart entitled "Examples of Acceptable Penicillin Schedules" advocated by the Venereal Disease Division of the United States Public Health Service is readily obtainable⁷² This provides at a glance the optimum treatment schedules recommended as a result of the aforementioned studies Reprints of the report on which it is based are available from the same source

The highest percentage of satisfactory results encountered in the treatment of early syphilis was reported from Bellevue Hospital⁷³ The series comprised only 59 patients, and they were treated with 26,666 units of penicillin G every two hours to a total of 2,400,000 units, satisfactory results were recorded in 58 cases, with a follow-up period of six months or more (98.2 per cent) With twice that dosage the satisfactory percentage was 97.3, and the author believed that most of the so-called failures were probably reinfections The data presented favored injections of penicillin G every two hours for ninety doses rather than every three hours for sixty doses, and suggested that a total of 2,400,000 units of penicillin was satisfactory in early syphilis A later report indicated no change in opinion⁷⁴

Confirmation of the superiority of a two-hour schedule of injections versus a three-hour interval is available from other sources⁷⁵ A three-hour schedule is advocated by the Mayo Clinic⁷⁶ Still other routines have been attempted, with varying degrees of success⁷⁷

Penicillin in oil As stated above, the United States Public Health Service survey strongly advised penicillin in oil and wax as the really practical method for the treatment of syphilis⁷¹ This method does not require hospitalization and is therefore suitable for office and clinic administration Ten daily injections totaling 6,000,000 units was the advocated dosage In a group of 802 patients receiving only 4,800,000 units over a period of eight days, 85.1 per cent satisfactory results were observed among 529 who were followed for nine months or more⁷⁸ The author believed that half the failures in this group were probably due to re-

infections Even without the estimated reinfections, a satisfactory average of 85.1 per cent is an improvement over the old standard chemotherapy results, since the over-all average for early syphilis by traditional therapy was approximately 75 per cent satisfactory results⁷⁶ There are two reports on a small group of patients who received only 300,000 units of penicillin in oil and beeswax daily for ten days, or a total of 3,000,000^{78 79} Of an original series of 238 patients, 136 were followed from three to eighteen months, with a failure rate of only 14 per cent This may have been somewhat optimistic since relapse is often not observed until after the first three months has passed Follow-up periods of not less than six months and preferably of a year or more are highly desirable before such a survey is presented

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

CASE 35101

PRESENTATION OF CASE

A twenty-two-year-old USO worker was admitted to the hospital complaining of frequent bloody stools, diarrhea, abdominal distention and increasing weakness.

The patient was in good health until four years before admission when occasional attacks of crampy lower abdominal pain and loose stools appeared, occurring two or three times each day. These continued without marked remissions or exacerbations for about a year. At that time, three years before admission, a fever appeared, the frequency of the bowel movements increased and the stools contained a little blood. She was hospitalized for a month, and a diagnosis of amebic dysentery was made, although the organism was not found. Diodoquin and emetine were employed with alleged improvement. After discharge she was somewhat improved but was extremely weak. She remained at home for two months and then was able to work. Two years before admission the attacks of diarrhea and abdominal, cramp-like pain recurred, and she was unable to continue working. Three months before admission, during a severe attack, she developed abdominal distention and ankle edema and she was admitted to another hospital. The edema and distention subsided, and she returned home on a low-roughage, low-fat and kapectate regime. Two weeks before admission the pain became more severe, and the stools were increasingly large, loose and bloody. The weakness and prostration became so great that she could not sit up in bed, and this precipitated her admission to this hospital.

For some time she had had frequent epistaxes and bleeding gums but no hematuria, hemoptyses, ecchymoses or jaundice. She had vague joint symptoms in the past. No menses had occurred for two years. At the age of fifteen a thyroidectomy had been performed for toxic goiter.

Physical examination showed an apprehensive, drowsy and somewhat incoherent patient in no acute distress. The skin was warm, dry and pale, the tongue was dry, slightly smooth and red. The

eyes were slightly prominent. Small, firm, non-tender, movable axillary nodes were palpable. The breasts were underdeveloped for her age, the pubic-hair pattern was normal. Both leaves of the diaphragm were high. The abdomen was very distended and tympanitic but flat in the flanks. No tenderness or spasm was present. The liver and spleen were not felt. Peristalsis was high-pitched but not tinkling.

The temperature was 99.2°F, the pulse 140, and the respirations 20. The blood pressure was 110 systolic, 40 diastolic.

The hemoglobin was 6.6 gm. The white-cell count was 16,200, with 80 per cent neutrophils, 12 per cent lymphocytes, 4 per cent monocytes, 3 per cent eosinophils and 1 per cent lymphoblasts. The red blood cells showed marked achromia and considerable variation in size. The urine showed a specific gravity of 1.012, with a ++ test for albumin and a ++ test for bile. Forty red blood cells and 10 white blood cells per high-power field were seen in the sediment.

The fasting blood sugar was 100 mg, the serum albumin 3.59 gm, and the globulin 1.87 gm per 100 cc. A prothrombin time was 28 seconds (control, 14 seconds). The chloride was 99, the sodium 136.8, and the potassium 5.9 milliequiv per liter. The nonprotein nitrogen was 44 mg per 100 cc, the van den Bergh reaction was 3.9 mg per 100 cc direct and 6.6 mg indirect. A blood Hinton test was negative. The stools were liquid and reddish dark brown, and no ova or parasites were seen. On proctoscopy the bowel wall was red and edematous. When wiped it was finely granular and bleeding. No large ulcerations were seen. An x-ray film of the abdomen taken with a portable machine demonstrated considerable distention of the stomach. Gas was also visualized in the ascending, transverse and descending colon.

The patient did poorly. Therapy included intravenous fluids, blood transfusions, chloromycetin, penicillin and sulfadiazine. Turpentine stipes were applied to the abdomen. Chloral hydrate, paraldehyde and demerol were employed for sedation. Abdominal distention increased, and peristalsis stopped. On the third hospital day icterus was noted, and the breath had a "mousy" odor. Multiple spider angiomas were seen on the anterior chest and neck. On the sixth hospital day the blood showed a serum albumin of 2.06 gm and globulin of 3.74 gm per 100 cc, sodium of 120.1, chloride of 90 and carbon dioxide of 18.4 milliequiv per liter. The van den Bergh reaction was 6.8 mg per 100 cc direct and 9.8 mg per 100 cc indirect, the prothrombin time was 26 seconds (control, 14 seconds), and a cephalin flocculation test was ++++ in twenty-four hours. In the evening the patient had a tonic convulsion, with the jaws clenched and the tongue between the teeth. This was relieved almost immediately by 10 cc of cal-

cium levulinate intravenously. On the following day the serum calcium was 6.5 mg per 100 cc, and the carbon dioxide 17.1, the sodium 125.8 and the chloride 92 milliequiv per liter.

She remained afebrile, but her condition rapidly deteriorated. Kussmaul breathing appeared, and the chest became full of rhonchi. The jaws were locked, an anesthesia airway was maintained. On the eighth hospital day she died.

DIFFERENTIAL DIAGNOSIS

DR MARIAN ROPES. This patient surely had involvement of at least three major systems: the gastrointestinal tract, the liver and the kidney. I will attempt to consider them separately and see whether or not they can be related and, if so, how.

The initial involvement was the gastrointestinal tract. I think that the entire history up to the time of admission is consistent with idiopathic ulcerative colitis. It is impossible to rule out other forms of colitis entirely on the record or by information that was available. Amebic dysentery cannot be ruled out entirely. There are a good many points against it, and the so-called response or partial response to treatment is not very impressive. It could have explained the apparent remission with a subsequent exacerbation after the remission. However, the strongest point against amebic dysentery is the proctoscopic examination showing a finely granular bleeding membrane and no ulcerations. The fact that ova or parasites were not identified does not rule out any of the parasitic diseases. Tuberculosis would have to be considered but can readily be discarded. The course would be extremely unusual with the relatively long period of remission. So I shall assume that the first part of the illness was due to idiopathic ulcerative colitis.

At the time of admission to the hospital the patient was perhaps somewhat sicker than one would expect from the degree of colitis that she had, and in the absence of fever at that time and with no more evidence of change in the sigmoid than was found. The only other things in the history before admission that might be mentioned are the vague joint symptoms in the past, which are consistent with ulcerative colitis. I believe, although I am not sure, that Dr Jones finds joint symptoms in 10 per cent of cases of ulcerative colitis. The joint symptoms vary greatly from arthralgia, which I judge she had, to true infectious arthritis or to a picture indistinguishable from rheumatoid arthritis.

Examination at the time of admission is consistent with ulcerative colitis. I think she probably also had arthritis, although we are not given enough information to be sure.

The laboratory findings are in general also consistent. The hemoglobin of 6.6 gm can be explained by the blood loss, which I judge had been rather great. The prolongation of prothrombin time could have been entirely secondary to the diarrhea and

associated with loss of vitamin K. On the other hand, it does suggest involvement of the liver, and in the presence of that and the elevated van den Bergh reaction liver involvement is strongly indicated. Similarly, the urinary findings and elevated nonprotein nitrogen surely suggest some renal involvement. For the moment I will not discuss that further but will go on with the gastrointestinal involvement. I have already mentioned the proctoscopy. To me that gives support to the diagnosis of ulcerative colitis.

We might see the x-ray films. I think the degree of distention of the stomach and intestinal tract is somewhat unusual. It makes me wonder if anything else ought to be considered with involvement of the gastrointestinal tract. I assume, however, that the distention was secondary to the colitis. I am interested also in the size of the liver and spleen.

DR STANLEY M WYMAN. The plain film of the abdomen shows the liver margin, and there is no evidence of gross change in the size of the liver. The lower margin of the spleen comes down an approximately normal distance. If anything, the spleen is slightly larger than usual. This is far from definite. The films of the colon show an extensive, finely granular ulcerating process, which begins in the rectum and extends throughout the entire length of the colon up to and involving the cecum. This is characterized by multiple, very tiny, spicule-like ulcerations, and the wall of the bowel appears to be thickened, suggesting that the process may have been going on some time. We have another plain film of the abdomen taken six months after the first, and there is a suggestion of an over-all, hazv density to this abdomen that raises, as Dr Ropes suggests, the possibility of fluid in the peritoneal cavity. I am not familiar with the technique employed on this film, which was made in another hospital, and perhaps that is a dangerous statement to make. The last film taken in this hospital is a portable grid film and shows the stomach filled with gas and rather large. It also shows, as the record states, gas in the transverse colon and some in the ascending and descending colon.

DR CHESTER M JONES. Any fluid?

DR WYMAN. I cannot make a statement because this film is inadequate.

DR ROPES. Surely the x-ray films are more than corroborative of a very severe ulcerative process in the colon of long duration. We know that she had it severely for two years and had some disease in the colon for four years. I am somewhat surprised at the degree of distention on admission and later the marked distention and stopping of peristalsis. I wondered at first whether or not she had had a perforation, but in the absence of other indicative signs I think it is unlikely and will assume that the distention and ileus were merely associated with the diffuse inflammatory disease.

The rest of the course following admission is, to my mind, a combination of the already present ulcerative colitis, with its severe constitutional reaction, and involvement of liver with apparent liver failure, and then some degree of renal failure. The convulsions occurring near the end were probably due to tetany. The calcium was 6.5 mg per 100 cc on the following day. We are not given the phosphorus values, and unfortunately we know too little about the urinary situation to say whether the tetany was due in part to renal involvement. It could have been due to the long-continued diarrhea, loss of vitamin D and loss of calcium over a long period, and may have been only secondary to the colonic disease. The convulsion was relieved rather rapidly with calcium, which is some corroborative evidence that it was due to tetany. It is true that the total protein was somewhat low, being under 6 gm per 100 cc, but if one adds another milligram to the calcium, it is still at a level at which we can assume that the ionic calcium was low enough to produce tetany.

The two other systems involved have to be considered separately at first. The liver was certainly involved. I should think there were only two possibilities that would relate the liver to the colonic disease. One is the liver disease associated with ulcerative colitis. As far as I know there is as yet no indication how they are related or what the etiology of the liver involvement is. It apparently varies in type. In this case the terminal course, I think, was due in large degree to liver failure. We have relatively little evidence whether or not there was any cirrhosis associated. I do not think that it could be diagnosed definitely from the available evidence, although it could not be ruled out.

The other possibility is to consider the presence of amyloidosis, which does occasionally occur in ulcerative colitis. Not too long ago a case was presented here with ulcerative colitis and associated amyloidosis. However, in the presence of both liver and renal involvement from amyloid I think it would be very unusual to have such a predominance of liver failure due to amyloid disease. Liver failure with amyloidosis has been reported and does occur but much less commonly than renal failure from amyloidosis.

Renal involvement was also definite. It may have been associated chiefly with a bleeding tendency, which was so apparent elsewhere, or the renal failure may have been secondary to the patient's general condition. On the other hand, with the information available I cannot rule out some primary renal involvement. I am unable to relate any renal involvement to disease of the colon unless it was due to bleeding or to amyloidosis.

In considering the underlying etiology of the whole picture there is little or nothing to suggest that any part was due to a neoplastic process. The majority of infectious processes can be ruled out.

The whole picture cannot be explained by tuberculosis. The colonic picture would be unlikely, and any such degree of liver involvement would be rare if not unheard of. I cannot rule out parasitic disease, but even if this were amebic colitis, which I doubt, the liver involvement would be an unusual form of amebic liver disease.

I believe that the best explanation is chronic idiopathic ulcerative colitis, with some unusual features, and the liver disease is that found in association with ulcerative colitis. The second most likely possibility is amyloidosis, explaining the liver and renal involvement secondary to what I consider ulcerative colitis.

DR DANIEL S. ELLIS: This patient was admitted with a diagnosis of ulcerative colitis, and she was so sick for the first two days that we did not immediately become aware of her liver involvement. As we began to get more and more of the story and to see her reaction and rapid deterioration it became apparent that we were dealing with liver failure and presumably cirrhosis of the liver, secondary to the ulcerative colitis.

DR JONES: I think one very interesting point was the terminal phase of the disease—the very striking acidosis that developed, with extreme Kussmaul breathing. I saw the patient several times with Dr. Ellis and I think this was one of the striking events in the last forty-eight hours—at least I would say she was practically comatose and breathing in a manner much like a diabetic person in deep acidosis. That was something I had not seen before that I can recall, at least to such a striking degree, in this type of combined inability of the liver and kidneys to work properly. One thing rather interesting, and I think it is probably a correct observation, was the sudden appearance of spider angiomas. I do not think she presented them when she came in.

DR ELLIS: This is hard to say. We did not even realize she was jaundiced when she came in. She was in a dark room, and not until we moved her to another room was the jaundice discovered. The situation in the abdomen during the first three days, as Dr. Ropes mentioned, made us wonder if she had intestinal perforation. She became more and more distended. Part of the distention we thought was due to medication. We asked Dr. McKittrick to see the patient since we felt we needed surgical advice. We could not be sure that she did not have an emergency within the abdomen.

DR TRACY B. MALLORY: I was impressed with the apparently sudden reversal of the albumin-globulin ratio in four or five days. I checked the figures with those in the record, and they are correct. I had never supposed it was possible.

DR JONES: I wondered about that.

DR ELLIS: Those are the correct figures. The only way we could explain it was on the basis of transfusions. She was well bled out. She had three

transfusions in twenty-four hours, and the second albumin figures were taken immediately after that.

DR JONES: What you pointed out is interesting and I think it all goes together. As I have already said, the sudden appearance of spider angiomas was very striking, and she did have a rapid and very dramatic deterioration of liver function and the drop in albumin may have reflected in part the loss of liver function as it progressed very rapidly.

Another striking thing was the sharp drop in sodium. This was replaced to a certain degree but we were never able to catch up. It dropped from 136 to 120 milliequiv per liter. There was almost a chemical upheaval in the whole picture. I suspect that the liver deteriorated very rapidly in a matter of a few days after having been about in balance for a long time.

DR LELAND S. MCKITTRICK: I have little to contribute because my decisions were very simple. In the first place, I do not think it possible to tell with accuracy whether or not perforation has occurred in a patient with ulcerative colitis. We have seen these patients with peritonitis from perforations when we could not tell when the perforation had occurred. She was very distended, and the first time I saw her she was slightly resistant and tender on the left side, but fortunately for any decision on my part, her general picture was such that one was not concerned about any surgical interference. It was obvious that her problem was not ulcerative colitis alone. This woman was sick from something else, and after these first few days it became reasonably apparent what that something else was. I have not seen, but perhaps Dr. Jones, Ellis or Ropes has, a patient with ulcerative colitis in whom the process in the liver was so precipitous and went on so rapidly as it did with this patient. This was almost like the liver deaths after an operation in the rapidity with which it moved along.

DR JONES: That is right. The picture that we used to see with acute yellow atrophy.

DR MCKITTRICK: And the so-called hepatorenal syndrome after surgery.

DR JACOB LERMAN: I should like to ask Dr. Wyman if the x-ray picture is consistent with amebic ulceration.

DR WYMAN: There is no specific characteristic picture of amebic ulcerations. This is more consistent, in my mind, with simple idiopathic ulcerative colitis.

CLINICAL DIAGNOSES

Ulcerative colitis, universal, chronic
Cholemia
Cirrhosis of liver
Cerebral hemorrhage?

DR ROPES'S DIAGNOSES

Ulcerative colitis, with associated liver involvement.
Cirrhosis of liver?

ANATOMICAL DIAGNOSES

Ulcerative colitis chronic
Cirrhosis of liver, post-atrophy type
Acute necrosis of liver, focal, disseminated
Pulmonary edema
Bronchopneumonia, bilateral
Anasarca

PATHOLOGICAL DISCUSSION

DR MALLORY: Autopsy showed an ulcerative colitis involving the whole bowel. Three liters of fluid was found in the peritoneal cavity, and the liver was small, grossly nodular and a little flaccid, but quite tough—very obviously a cirrhotic process. The nodules of regeneration ranged from 2 to 8 mm in diameter, a wider range than one usually sees in the common type of fatty, so-called alcoholic cirrhosis. The nodules of liver parenchyma were sharply circumscribed and embedded in large and extensive areas of scarring in which many bile ducts were present. There were also, at the edges of these nodules, hemorrhagic extravasation and fresh necrosis of liver cells. So I think we can classify this cirrhosis without any question as the post-necrotic type that follows a healed atrophy, and there was also evidence of the recurrence of that process in the form of fresh, massive necrosis just within the last few days before death. There was severe, terminal, pulmonary edema and bronchopneumonia.

This development of liver disease in association with ulcerative colitis is of considerable interest and, as Dr. Ropes has pointed out, not very much is known about it. Four out of five patients dying of ulcerative colitis show at autopsy a massive, fatty infiltration of the liver, and an occasional case will show diffuse, fatty cirrhosis, essentially similar to that seen in chronic alcoholism. This is the other type of portal cirrhosis that appears to follow an attack of massive atrophy. Himsworth and Glynn,* in the last four or five years, have made the claim that post-necrotic cirrhosis can result from dietary deficiency. A good many people who have attempted to repeat their experiments have had very little success in so doing, and it is very difficult to find any distinct proof in the field of human pathology that atrophy of the liver has resulted from dietary insufficiency. A case of this sort might be cited as evidence, but there are so many other factors—for instance, the strong element of infection and multiplicity of drugs with which she was treated—that it is inconclusive.

DR JONES: What did the kidneys show?

DR MALLORY: As far as we could tell, they were essentially normal, slight dilatation was noted in Bowman's capsule and minimal, if any, changes

*Himsworth H. P., and Glynn L. E. Massive hepatic necrosis and diffuse hepatocytolysis (acute yellow atrophy and portal cirrhosis) their production by means of diet. *Clin. Sc.* 5:93-125, 1944.

in the tubules. So I think that the renal insufficiency was secondary to the liver condition.

DR JONES: Do you think that is the case in the hepatorenal syndrome? A certain group have kidney damage, but a great many show evidence of inadequate renal function in relation to hepatic failure.

DR ELLIS: Was the brain examined?

DR MALLORY: Yes, and it was normal.

CASE 35102

PRESENTATION OF CASE

A twenty-nine-year-old man was transferred to this hospital because of diarrhea and jaundice.

Since the age of fourteen he had suffered recurrent bouts of frequent loose stools. Approximately two years before entry he was treated by his physician over a period of three months because of nausea, headache and slight increase in diarrhea. At the end of this time it was noticed that he was jaundiced and that the urine was dark. There was loss of weight and appetite, and the liver was large and tender. He improved and returned to work, but one month later he was found to have anemia, for which he was given transfusions. The weight had fallen from 160 to 140 pounds, and there were signs of fluid in the right side of the chest. The liver edge was palpable three fingerbreadths below the costal margin. The temperature was 99°F. There was no jaundice, ascites or peripheral edema. He was instructed concerning a high-protein, high-carbohydrate diet and rest and, although he was advised to return more frequently to his physician, he was not seen again until about six weeks later, when, aside from a 15-pound weight gain, physical findings were essentially unchanged.

He returned to work for two and a half months when, following an attack of gastroenteritis, diarrhea became very severe. Again, a macrocytic anemia required several transfusions. During the next six months he became progressively worse and was finally admitted to another hospital. At this time he was semidelirious, and the temperature was 104.5°F. Gynecomastia, spider nevi and superficial abdominal varices were present. Sigmoidoscopy revealed diffuse petechial ulcerations and edema of the sigmoid and rectal mucosa. There was slight contracture of the mucous membrane in one area, and polypoid changes were noted in the sigmoid. The feces showed no enteric pathogens or parasites. There was 50 per cent retention of bromsulfalein, the serum van den Bergh showed a delayed positive reaction, and the prothrombin time was 45 per cent of normal.

In the hospital he was given transfusions, sulfasuxidine, penicillin and a high-protein, high-carbohydrate diet. Three months later he was admitted to another hospital, where on physical examina-

tion he was found to have a right hydrothorax, ascites, jaundice and a temperature of 102.6°F. The white-cell count was never above 4200, and neutrophils were never over 26 per cent. The total protein was 6.1 gm, with an albumin of 2 gm and a globulin of 4.1 gm per 100 cc. A bromsulfalein test showed 35 per cent of the dye retained in thirty minutes. Under a regimen of rutin, vitamin K, streptomycin, crude liver extract, vitamins and high-protein, high-carbohydrate diet he did well. The fever and jaundice disappeared, the ascites and hydrothorax became less marked, and appetite improved. Against the advice of his physician the patient was discharged after three weeks in the hospital. He had barely returned home, however, when diarrhea became very marked. Within a few days the temperature rose to 104°F, and he was disoriented. Five weeks later he was readmitted to the same hospital, where, with the exception of jaundice, he exhibited the physical findings of the previous admission but to a much greater degree. In addition to the previous therapy, intravenous albumin and mercurhydrin were administered. The course, however, was progressively downhill. Repeated thoracenteses, with the removal of 2000 or 3000 cc of yellow fluid, were necessary. Never a co-operative patient, he became even less so, refused food and fluids, and cursed and struck the nurses. For one week he was psychotic and unresponsive. Stools usually averaged four to eight daily, but at times there were ten to fifteen per day, with or without blood, although there was never any great loss of blood. At the end of two and a half months it was impossible to obtain nurses for him and practically impossible to treat him because he refused all forms of medication.

A history, later obtained from the patient's father, disclosed that his parents had been divorced for many years and that his marriage had also been unsatisfactory, a separation having taken place six months before admission. Apparently the patient was a headstrong person, and it was noted that arguments with the family were often followed by bouts of diarrhea. He did not drink alcoholic beverages.

On admission to this hospital physical examination revealed a semicomatose, emaciated, chronically and critically ill young man lying quietly in bed and occasionally groaning or crying out. There was clubbing of the fingers and dullness to flatness over the right chest. The cardiac impulse was forceful and diffuse, and the liver edge was palpated two or three fingerbreadths below the costal margin. Gynecomastia and testicular atrophy were present. There was no jaundice or peripheral edema.

The temperature was 99°F, the pulse 120, and the respirations 27. The blood pressure was 88 systolic, 55 diastolic.

The urine gave a + test for albumin, and the sediment was loaded with red blood cells. The

blood hemoglobin was 10.5 gm, the white-cell count was 4200, with 23 per cent neutrophils, 58 per cent lymphocytes, 12 per cent monocytes and 2 per cent eosinophils. The red blood cells showed moderate variations in size, and the platelets were normal. The serum protein was 6.5 gm per 100 cc, with 2.5 gm of albumin and 4.02 gm of globulin, and the albumin-globulin ratio was 0.6. The non-protein nitrogen was 23 mg per 100 cc, the chloride was 101, the sodium 131.4 and the potassium 3.9 milliequiv per liter. A cephalin flocculation test was ++ in twenty-four hours and ++++ in forty-eight hours. The prothrombin time was 27 seconds (normal, 16 seconds). The stools were light tan and guaiac negative.

During the first hospital week the patient remained critically ill despite frequent transfusions, intravenous albumin, streptomycin, mercurhydriol and other supportive therapy. During brief periods of consciousness he was most resistant to anything being done for him. Most of the time he was irrational, semicomatose or in frank coma. Proctoscopy revealed scattered polyps and a granular mucosa, which bled profusely on the slightest trauma. A biopsy of one of the polyps was later reported as pseudopolyp and chronic ulcerative colitis. During the next several days he showed considerable improvement to such a degree that on the evening of the fourteenth hospital day he read magazines and talked about future plans. On the following day an ileostomy was performed. Postoperatively he did fairly well until the third day, when he complained more severely of abdominal pain. On physical examination he was irrational and had grunting respiration. The ileostomy, which had more recently drained poorly, was found prolapsed but still viable. There was abdominal distention, a fluid wave and absent peristalsis. The right side of the chest showed more fluid than before. The temperature was 103.5°F. The blood hemoglobin was 10.5 gm, the white-cell count was 3800. The blood sodium was 132.2, the chloride 96, the potassium 3 and the carbon dioxide 27.9 milliequiv per liter. Jaundice and peripheral edema became marked, and the left side of the chest, which had been clear all during hospitalization, showed many rales. He remained in coma with gasping respirations and was found dead in bed on the fourteenth postoperative day.

Throughout the patient's stay in the hospital the urine showed + or ++ test for albumin, and the sediment contained 15 to 30 red blood cells and 3 to 5 white blood cells per high-power field. The highest white-cell count recorded was 6500, and most counts were in the range of 3600. Therapy consisted of transfusions, intravenous fluids, streptomycin, penicillin, ampicillin and other supportive measures. There was excellent response to the several injections of mercurhydriol given. Repeated paracenteses were of little benefit.

DIFFERENTIAL DIAGNOSIS

DR REED HARWOOD From the onset of the jaundice to the time of death it was evident that this patient had two severe diseases—the disease of the colon and that of the liver. I think the history of the last two years merely records the downhill course and progress of these two diseases, with each making the other worse. We are told very little about the onset. I shall try to reconstruct what may have happened at that time.

I imagine that the physician taking care of him saw him at home, and that the patient had vague complaints. The doctor was not quite sure what part of the body was involved or what the diagnosis was. I would guess that he paid most attention to the diarrhea—he probably gave the usual mild, supportive measures for the diarrhea and did not realize that he was dealing with something extremely serious until the jaundice appeared. He then looked back and wondered what was the cause of the jaundice. Here are the possibilities that occurred to me, not listed in the order of probability but as I thought of them. Virus hepatitis. Perhaps these vague complaints of headache, nausea and anorexia represent mild hepatitis, with little or no jaundice. Virus hepatitis can relapse and perhaps at the end of two or three months, with his poor nutritional state from diarrhea, he had an exacerbation during which the jaundice developed. Toxic hepatitis of some sort is another possibility. Such chemicals as cinchophen, sulfonamides, anti-amebic medication or possibly some industrial solvent to which he had been exposed may have been responsible. I wondered also whether ulcerative colitis could produce such severe liver failure. I decided that it probably did not in this case. From the history we do not get the impression that he had a severe ulcerative colitis or that he was in a severely depleted state at the time the jaundice developed.

Then, of course, I thought of amebiasis as an explanation for the whole picture. We know that amebiasis will cause diarrhea, we know that amebas can invade the liver, where they cause a severe hepatitis, and also that amebic abscess can rupture from the liver through the diaphragm into the lung. But from all I can find out about amebic hepatitis, it does not fit the picture here. Amebic hepatitis is a severe disease, the patient is acutely ill, with a high fever and a high white-cell count. The same statement can be made of amebic abscess in the lung. I am sure this patient would have been sent to the hospital if he had such alarming manifestations. Although I cannot rule it out, I am quite confident that amebic hepatitis will not be found. So we come to the conclusion that we are dealing with two diseases—chronic idiopathic ulcerative colitis and hepatitis with cirrhosis, probably the coarsely nodular type of cirrhosis, with the etiology of the hepatitis undetermined.

Several details of this case warrant brief comment. The appearance of the hydrothorax one year

before the ascites puzzled me. I cannot attempt to explain it. Another point that bothered me was the low white-cell count, the granulocytopenia in the face of severe sepsis in the terminal stages. I find difficult to explain. It may be that as a result of chronic, wasting disease, the bone marrow was depressed. Possibly the granulocytopenia was due to drugs. He must have had a great many different kinds of drugs. Perhaps the sulfonamides were responsible. I thought of some blood dyscrasia such as leukemia but ruled it out. Then there was the testicular atrophy, the low blood pressure and the low blood sodium, all of which made me wonder if that combination could be added up to adrenal failure. The hematuria I ascribed to the prothrombin deficiency. I considered other diseases, including amyloid disease, tuberculosis and cancer of the liver or bowel, and decided that they did not play an important part. As for the final episode, one cannot say whether or not he had a perforation with peritonitis toward the end. I think it is very likely that he had bronchopneumonia.

DR J. H. MEANS: I think the endocrine part of the disease is interesting. He had gynecomastia and testicular atrophy. I would be interested in knowing about the pubic, axillary and body hair in relation to liver disease. There is nothing about that in the abstract.

DR DANIEL S. ELLIS: They were quite normal.

DR MEANS: What causes these signs when they do occur? Is it because the liver does not bring down estrin normally?

DR ELLIS: I do not know, but that is one of the theories.

When this patient was admitted we knew he had liver disease. The liver was palpable, and everyone thought it was nodular. We thought we were dealing with advanced cirrhosis to begin with and considered the question of how much one could salvage and whether one should attempt to operate on him as a supportive measure. An ileostomy was performed, and the liver did not have enough reserve to make the grade, and we thought his death was primarily that of liver failure.

CLINICAL DIAGNOSES

Chronic ulcerative colitis
Cirrhosis of liver

DR HARWOOD'S DIAGNOSES

Chronic idiopathic ulcerative colitis
Hepatitis, with coarsely nodular cirrhosis

ANATOMICAL DIAGNOSES

Chronic ulcerative colitis, with pseudopolyposis and adenocarcinoma
Portal cirrhosis of liver, post-atrophy type
Ascites
Operation ileostomy
Intussusception, with gangrene of terminal ileum

PATHOLOGICAL DISCUSSION

DR TRACY B. MALLORY: Autopsy on this man showed a liver within normal weight limits, 1700 gm, but coarsely nodular, with some of the nodules measuring 15 mm in diameter. This microscopical preparation shows one of the relatively large areas of regeneration and here a wide band of scar tissue. Most of the nodules of liver cells are sharply outlined as if encapsulated, and there is no invasion of fibrous tissue into the periphery.

There was in this case no clear-cut terminal necrosis. There was extensive ascites, 5000 cc, and an unusual complication of the last few days of life was an intussusception of the distal end of the ileum beyond where it had been transected to form the ileostomy. Finally there was incipient peritonitis.

This is obviously another case of post-necrotic type of cirrhosis. One additional etiologic factor in this case was the suggestive history of epidemic hepatitis. In retrospect one cannot say it was or was not, it might have been.

DR CHESTER M. JONES: I am sorry that Dr McKittrick is not here to comment on the ileostomy. At the time it was perfectly obvious that if the patient was to be helped at all, ileostomy had to be done, but it was impossible to arrive at a point when the patient would tolerate any such maneuver. When he came in it was quite obvious that he was desperately sick. It seemed we had to take the chance to make a situation whereby the ulcerative colitis and nutrition could be controlled and, by so doing, possibly to be able to stop the progression of the process in the liver long enough to get him in some sort of decent condition—obviously, a desperate move. Everyone realized it and did not expect to get away with it.

DR ALFRED KRANES: What was the colon like?

DR MALLORY: It showed a severe, chronic, ulcerative colitis with marked polyp formation. We see three kinds of polyps in patients with longstanding ulcerative colitis. Some of them are mostly inflammatory in character and are called pseudopolyps—a sort of hypertrophy of the remaining fragments of mucous membrane. We sometimes see true neoplastic polyps, and in some cases frank carcinoma develops. The biopsy on this patient we reported as a pseudopolyp, and at autopsy sections were taken from two or three other lesions by hazard, one of which proved to be carcinomatous. So nothing less than a total colectomy would have helped him for very long.

DR HARWOOD: How about the adrenal glands? Did they show anything?

DR MALLORY: No.

DR JONES: I think it is important to point out that patients with ulcerative colitis going a good many years, more than ten years, run a definite hazard of developing carcinoma. It is often impossible to be certain about this diagnosis because the blood in the stools is assumed to be due to the colitis.

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MASSACHUSETTS FIVE-YEAR PLAN

MORE than 600 panel participants and delegates from a number of representative organizations met together in the first Massachusetts Health Conference, held at the Hotel Statler on February 19 and 20 for the purpose of discussing means of improving health in Massachusetts during the next five years. Agencies represented ranged from the Ladies Garment Workers Union to the Junior League and from the Massachusetts State Nurses Association to the Committee for the Nation's Health.

Nineteen panels were conducted, the majority of them holding sessions both morning and afternoon on the Saturday and Sunday of the Conference. Such topics were fruitfully discussed as

accidents and their prevention, citizen participation in state and community planning, dental health, environmental sanitation, health problems of the aged, hospital problems, industrial health, maternal and child health, medical-care costs and methods, mental health, nursing problems, rural health problems and school health, and others of no less importance.

At luncheon on the first day Dr Clifton T. Perkins, Commissioner of Mental Health, told of the problems of his department and the opportunity that an increased budget and improved personnel will give for the transformation of its objectives from custodial care to active treatment and the prevention of mental disease. In the evening the Hon. John F. Kennedy, congressman from the eleventh Massachusetts District, addressed the dinner audience, and at luncheon on the following day Dr Charles F. Wilensky, president of the American Public Health Association, and His Excellency, Governor Paul A. Dever, spoke to the Conference. Dever announced in particular that the first claim considered by him of all those made for state funds was for the physically and mentally ill citizens of the Commonwealth.

As the report of each panel chairman was made at the close of the Conference, the result of the co-operative and constructive discussion that each problem had received became evident and the contributions that could be made by lay as well as professional participants. Of special interest were the meetings of the most largely attended group, that on medical-care costs and methods, under the chairmanship of Dr. Hugh R. Leavell, professor of public-health practice of the Harvard School of Public Health.

Discussers in the field covered by this panel varied from representatives of the Department of Public Health and the Massachusetts Medical Society to those from Blue Shield, the Committee for the Nation's Health and the CIO. Agreement on all particulars was naturally impossible, but discussion was free, frank and friendly. The steering committee of the panel in its final statement approved making adequate medical care "available to everybody, regardless of income, race, color, creed or national origin," the term to include the

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There was in this case no clear-cut terminal necrosis. There was extensive ascites, 5000 cc., and an unusual complication of the last few days of life was an intussusception of the distal end of the ileum beyond where it had been transected to form the ileostomy. Finally there was incipient peritonitis.

This is obviously another case of post-necrotic type of cirrhosis. One additional etiologic factor in this case was the suggestive history of epidemic hepatitis. In retrospect one cannot say it was or was not, it might have been.

DR CHESTER M JONES: I am sorry that Dr McKittrick is not here to comment on the ileostomy. At the time it was perfectly obvious that if the patient was to be helped at all, ileostomy had to be done, but it was impossible to arrive at a point when the patient would tolerate any such maneuver. When he came in it was quite obvious that he was desperately sick. It seemed we had to take the chance to make a situation whereby the ulcerative colitis and nutrition could be controlled and, by so doing, possibly to be able to stop the progression of the process in the liver long enough to get him in some sort of decent condition—obviously, a desperate move. Everyone realized it and did not expect to get away with it.

DR ALFRED KRANES: What was the colon like?

DR MALLORY: It showed a severe, chronic, ulcerative colitis with marked polyp formation. We see three kinds of polyps in patients with long-standing ulcerative colitis. Some of them are mostly inflammatory in character and are called pseudopolyps—a sort of hypertrophy of the remaining fragments of mucous membrane. We sometimes see true neoplastic polyps, and in some cases frank carcinoma develops. The biopsy on this patient we reported as a pseudopolyp, and at autopsy sections were taken from two or three other lesions by hazard, one of which proved to be carcinomatous. So nothing less than a total colectomy would have helped him for very long.

DR HARWOOD: How about the adrenal glands? Did they show anything?

DR MALLORY: No.

DR JONES: I think it is important to point out that patients with ulcerative colitis going a good many years, more than ten years, run a definite hazard of developing carcinoma. It is often impossible to be certain about this diagnosis because the blood in the stools is assumed to be due to the colitis.

hands the intimate history of one of the greater figures of American history is for the first time fully disclosed

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VETERANS ADMINISTRATION HOSPITAL PROGRAM

THERE has been considerable confusion about the treatment not only of disabled veterans and their dependents but also of those suffering from nonservice-connected disabilities or illness. As a recent release from the Veterans Administration states, many wives and families of veterans were treated by Army and Navy doctors, while their husbands were on active duty, as a result of what is almost a service tradition. For many years, families of personnel in the armed forces obtained treatment from Army or Navy physicians if it were "more practical" for such service to be rendered by these physicians. Some wives now erroneously believe that they are also entitled to medical treatment from Veterans Administration physicians.

Men and women who served in the armed forces, except those with dishonorable discharge, are entitled to hospital treatment in the following categories: emergency cases, those suffering from injuries or diseases incurred in or aggravated by military service, and those who state under oath that they are unable to pay hospital charge for treatment of nonservice-connected disabilities or illnesses. Veterans in the last classification, if not in the emergency class, must wait until a bed becomes available. Treatment is available for veterans with service-connected disabilities, but in other cases each veteran's eligibility must be determined by the Veterans Administration itself before treatment of this type can be authorized.

These limitations are of considerable interest in view of the prospective hospital expansion program, which may be used as a political argument to spend more of the taxpayers' money wastefully and ill-advisedly. Studies in the past three years have

indicated a need for a change in this program, the estimated requirements for hospital beds made during and immediately after the war were considerably larger than has proved necessary. Admission policies have been such that more than two out of three patients were and still are admitted to hospitals for nonservice-connected ailments.

As a result of the careful studies of 64 individual projects not yet under contract, the President has ordered a reduction of 16,000 beds. To effect this, the Veterans Administration plans the cancellation of 24 proposed new hospitals and reduction in the size of 14 others, a change in program that "will not result in a single service-connected veteran being denied immediate hospitalization."

There is another factor. Owing to the shortage of professional personnel, the Veterans Administration is having great difficulty in properly staffing its present hospitals. The estimated maximum load of patients with *service-connected* disabilities is about 51,000, which even at present, leaves more than twice as many additional beds available to the other veteran patients. "In the light of more than three years' experience since the end of World War II," according to the release, "it is evident that the estimates of bed requirements were considerably too high. To construct new hospitals which we cannot staff and therefore, cannot put into use would be an indefensible waste of public monies."

This report states further that the proposed elimination of new beds would result in a saving of \$280,000,000. With many hospitals running at a prohibitive annual deficit, it seems that the medical profession has here a splendid opportunity to exert its influence in constructive suggestions that will help to relieve the present critical condition of some civilian hospitals in which nonservice-connected cases should be cared for, but at the same time, steps should be taken to ensure that the care given for *service-connected* injuries and illnesses of the veteran remains the best that can be obtained.

FIRST BOOK ON RICKETS

DANIEL WHISTLER, an Englishman, in 1645, presented to the University of Leiden for the degree of doctor in medicine a dissertation entitled *De*

services of "physicians, dentists, pharmacists, nurses, medical social workers and other professional persons, the services of clinics, hospitals and related facilities and the supply of necessary drugs and appliances"

The use of voluntary prepayment group health plans was encouraged, it was admitted that the people have also the right, "if they deem it wise," to establish a system of governmental health insurance. A resolution was passed unanimously disapproving the senseless slaughter of "tens of thousands of unwanted animals in public pounds," when they were so desperately needed for medical research.

It may fairly be said that the success of the Conference exceeded the fondest hopes of its sponsors, improved relations and better understanding of mutual goals by diverse interests should result

BENJAMIN RUSH AND HIS TRAVELS THROUGH LIFE

IN 1800, Benjamin Rush, the energetic, quarrelsome physician and patriot of the American Revolution, then fifty-five years of age, began to write his autobiography, *Travels through Life*, having just seen through the press his *Essays, Literary, Moral, and Philosophical*. His active and exciting life brought him many memories of his student days, early years of practice in Philadelphia, the Revolution and his part in the Declaration of Independence, his bitter fight for reform in the military hospitals, the yellow-fever epidemic of 1793, and his battle with William Cobbett, then subsiding after Cobbett's departure from America in June, 1800. *The Rush Light*, a harsh pamphlet published by Cobbett, was rapidly dimming, and Rush could turn to a calmer period of reflection, practice and the teaching of medicine, all gifts with which he was highly endowed, and to his account of his private life. His written word, long in manuscript or imperfectly printed, has now been issued in a complete and unexpurgated edition under the meticulous and scholarly hand of George W. Corner, along with the "Commonplace Books" or diaries for 1789-1813.¹

First taught in 1761 as a private pupil of John Redman, Rush later attended the lectures of Shippen and Morgan from 1762 to 1765, when the school of medicine of the University of Pennsylvania was in its infancy. He went abroad in 1766, listened to lectures in Edinburgh, brushed up on his Latin, taught himself Italian and Spanish, and received his medical degree two years later. After further training in St. Thomas's Hospital in London and a visit to Paris, Rush returned to Philadelphia in 1769, developed a successful practice, advocated the abolition of slavery, became an active patriot with Thomas Paine, John Adams and Thomas Jefferson, signed the Declaration, served for a short and stormy period as surgeon-general of the armies of the Middle Department, lectured at the medical school and, after 1789, devoted himself primarily to his profession. Basing his views on those of William Cullen and John Brown, he developed a "system" of treatment, calling for "depletion" by thorough bleeding and purging, a theory that came to hold for his speculative mind all the fascination of an ultimate panacea. When his method was applied in the yellow-fever epidemic, Rush claimed superior effectiveness, but he failed to keep exact records of his own cases and he did not even use the vital statistics of his day. Cobbett, a lay critic, soon discovered the weakness of Rush's treatment, and, although Rush was not guilty of deliberate misrepresentation, a modern evaluation of his work indicates that he was "rather the victim of a certain credulity about diagnoses and cures which characterized much of his work."² He was, in other words, an observant man, but not a good observer.

Rush's autobiography is not a very readable volume, but factually it is an outstanding record of his times, a "Philadelphia Story" of distinctive merit, clearly told, without retraction or hesitation. Of his medical enemies he speaks with no malice, for he was at heart a lover of peace and of his fellow citizens.

The numerous footnotes by Corner are authoritative and always helpful, the index is fully adequate, and the book is a great credit to the American Philosophical Society, the holder of the original manuscript, and its able editor, in whose

CROKE — Louis W. Croke, M.D., of Dorchester, died on February 15. He was in his sixty-fourth year.

Dr. Croke received his degree from Tufts College Medical School in 1911. He was formerly staff surgeon for Liberty Mutual Insurance Company and was a fellow of the American Medical Association.

A sister survives.

NOTES FROM THE MEDICAL EXAMINER

BARBITURATE TOXICITY

The rapid and accurate quantitation of barbiturates in blood and tissue has been made feasible in the past three years by the development of methods utilizing the ultraviolet spectrophotometer.^{1,2} These require only 5 to 10 cc of specimen, and it is possible for the first time to determine the blood barbiturate concentration of a comatose patient in the emergency room as well as that of a dead person whose residual concentration is very low.

CORRELATION OF BARBITURATE LEVEL WITH STATE OF CONSCIOUSNESS

Preliminary studies of the concentration of pentothal in the blood during surgical anesthesia² show that consciousness is lost at about 1.0 mg per 100 cc, whereas second-plane anesthesia is reached at 2.0 to above 3.0 mg per 100 cc.

The short-acting barbiturates, seconal, amytal and pentobarbital, cause coma when the blood level is between 1.0 and 3.2 mg per 100 cc. Consciousness is lost at slightly lower levels when larger doses are ingested — that is, with rapidly rising drug concentrations in the blood. Another important modifying factor is the state of reflex excitability of the central nervous system; a given blood concentration is less depressing in agitated patients or those stimulated by benzedrine or caffeine.

The long-acting barbiturates, barbital and phenobarbital, are much less potent than those mentioned above. Several conscious patients, some of whom were ambulatory, were found to have blood levels as high as 5.0 to 7.5 mg per 100 cc. Two patients with blood phenobarbital levels of 7.2 and 6.8 mg per 100 cc were described clinically as semicomatose. The minimum blood barbiturate concentrations accompanied by coma in 7 patients who recovered from barbital or phenobarbital poisoning were in the range 7.0 to 12.0 mg per 100 cc.^{4,5}

FATAL CONCENTRATIONS OF BARBITURATE

In the evaluation of a post-mortem blood barbiturate level as the cause of death five principal variables must be considered. These are the identity (potency) of the barbiturate concerned, the time elapsed from ingestion of the drug until death, the presence of concomitant alcoholism or central-nervous-system depression by other agents, the effects of therapy and complications of which

respiratory infections and renal failure are particularly noteworthy.

The higher potency of the short-acting barbiturates, as compared to barbital and phenobarbital, is well exemplified in a series of 10 cases, all fatal without therapy and none complicated by alcoholism.^{4,6} Seven deaths resulted from poisoning by seconal, pentobarbital, amytal or combinations of these agents. The post-mortem blood barbiturate concentrations were 2.0, 3.7, 4.0, 4.8, 6.6, 7.2 and 7.5 mg per 100 cc. The others were phenobarbital and barbital poisoning, and the levels were 9.8, 12.0 and 34.0 mg per 100 cc. It should not be inferred, however, that the finding after death of a blood barbiturate concentration of 2.0 mg per 100 cc of a short-acting or of 9.8 mg of a long-acting barbiturate constitutes *prima facie* evidence of death from barbiturate poisoning. Recovery has been observed after barbiturate levels of 5.1 mg of pentobarbital, 12.8 mg of phenobarbital and 20.6 mg per 100 cc of barbital.

The time factor is of importance in two respects. Death may occur in the early hours of barbiturate poisoning with relatively low blood levels of the drug if the concentration is rising rapidly. In the first case of the short-acting series cited above, death occurred within four hours of ingestion of the drug with over 65 gr (4.3 gm) of seconal still in the stomach. On the other hand, barbiturates share with carbon monoxide and alcohol the property of producing irreversible asphyxial damage to the brain and then being partly or completely destroyed or excreted before death ensues. One young woman succumbed five days after ingesting a fatal dose of seconal although no barbiturate was demonstrable in the blood on the third day.

Experimental and clinical evidence of a "synergistic toxic action" of barbiturates and alcohol has been published,^{7,8} but the dangers inherent in indiscriminate use of combinations of these agents deserve re-emphasis. Seven deaths due to the combination of alcohol and barbiturate, although neither drug was present in ordinarily fatal concentrations, have been encountered in recent years by members of the Department of Legal Medicine at the Harvard Medical School. Goldbaum's⁹ terse note ("Alcoholic Died soon after injection of 100 mg of sodium amytal I.V.") is probably a further example of this kind.

Although consideration of therapy is beyond the scope of this communication it appears that general supportive therapy including oxygen, intravenous fluids to the limit of tolerance and the common stimulants are of greatest importance; picrotoxin and other convulsants should be employed with great caution lest their toxic effects be added to the barbiturate poisoning, and the use of succinate, ascorbic acid and so forth is still in the experimental stage.

morbo puerili Anglorum, quem patrio idiomate indigenae vocant "The rickets" This is the first book on the subject, and the first use of the word rickets In 1684, Dr Whistler issued a second edition, said to be improved because of imperfections in the original example

In 1884 Moore,¹ writing on Glisson's² treatise on rickets, published in 1650, devotes considerable space to a discussion of Whistler's small disputation and at first believed that it was not authentic and did not exist until it was called to his attention that a copy of the 1645 imprint had been discovered in the Library of the Royal College of Physicians of London

Whistler did not lay claim to the discovery of the disease but referred to it for the first time as the rickets, a name locally applied for some twenty-five years Moore was highly critical of Whistler and his work and brought out that Glisson and a group of co-workers had been engaged on an investigation of the disease since 1645, culminating in the publication of Glisson's book in 1650 It was intimated that Whistler rushed into print for the purpose of forestalling Glisson's book Whistler's description of the disease is a concise and clear statement of most of the then known facts and appears to have been based on personal observations³ Both editions are very scarce although three copies of the 1645 edition have been located in British libraries — in the British Museum, in Merton College, Oxford, and in the Royal College of Physicians, London Likewise, there should be copies in the University of Leyden and other European libraries

Recently the Boston Medical Library has acquired a copy of the 1684 imprint with an English translation, and a beautiful facsimile reproduction of the 1645 edition made from the copy in Merton College The facsimile bears no indication of date or printer or that it is a reproduction, but it is known that it was done late in 1948 for Dr Alexander Cook, of Oxford, and that only a few copies were struck off for his friends The Library is indebted for its copy to a good friend and fellow of the Library

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MASSACHUSETTS MEDICAL SOCIETY

WOMAN'S AUXILIARY

The Executive Committee of the Woman's Auxiliary of the Society held its mid-winter meeting at the Algonquin Club, 217 Commonwealth Avenue, Boston, on January 21 as luncheon guests of the President

Present were the officers of the Auxiliary Mrs Leighton F Johnson, president, Mrs Charles E Ayres, vice-president, Mrs John F Conlin, corresponding secretary, Mrs Andrew Nichols, III, recording secretary, Mrs Leo G Rondeau, treasurer, the presidents of the ten district auxiliaries Mrs Oscar S Simpson, Barnstable, Mrs Curtis B Kingsbury, Bristol North, Mrs Harold R Kurth, Essex North, Mrs John J Pallotta, Essex South, Mrs Albert E Morris, Middlesex East, Mrs John F Casey, Middlesex South, Mrs George W Papen, representing Mrs J J Hepburn, Norfolk, Mrs Thomas H Lanman, Suffolk, Mrs Charles E Ayres, Worcester, Mrs William G LeBrecht and Mrs John J Curley, representing Mrs L B Thompson, Worcester North, and the chairmen of the state committees Mrs Chester S Keefer, Education, Mrs Roger I Lee, Public Health, Mrs Howard F Root, Legislation, Mrs Reginald H Smithwick, Hospitality, Mrs John W Spellman, Benefits, and Mrs George G Bailey, Nominations Mrs Benjamin Alexander, chairman of the Program Committee, was unable to attend

Dr John F Conlin, director of Medical Information and Education, spoke on national legislation, outlined the plans for the Massachusetts Health Conference, and announced that an appropriation of \$500 would be requested of the Council of the Massachusetts Medical Society for the use of the Auxiliary during 1949

Each president was asked to appoint two delegates and two alternates to attend the Health Conference Mrs Root reported on bills affecting health that had been introduced to the General Court, and Mrs Ayres spoke about the part that the Auxiliary would take in the annual meeting of the Society in Worcester, May 25, 26 and 27

The Auxiliary of the Worcester North District Society, organized on January 14, was welcomed to membership, and plans for a speaker's bureau were discussed

DEATHS

BRUNELLE — Pierre Brunelle, M.D., of Lowell, died on February 11 He was in his seventy-seventh year Dr Brunelle received his degree from McGill University Faculty of Medicine in 1896 He was a former president of the Massachusetts Medical Society and was formerly a member of the Lowell Board of Health His widow, a son, two daughters and a sister survive

claiming them," you are stooping to impugn the motivation of these critics without any possible justification. This is a form of *argumentum ad hominem* that can only serve to weaken the force of your remarks.

Your point that many of us members of the American Medical Association have been very negligent in the matter of taking political action at the grass roots is accurate and justified. I hope it will produce a high percentage of attendance at, and of activity in, all district-society meetings. However, when you try to shut off efforts at reform by approaches directed at higher levels, with the trite bromide that it is a dirty bird that fouls its own nest, I submit that you are descending to a low level of editorial writing.

It has been repeatedly claimed that organized medicine is democratic. I won't dispute this, but may point out that we can easily find in the world today various interpretations of the word "democratic." However, I will submit that in the American variety of democracy, free speech is one of the rights of man. The constitution of the United States abundantly protects the right of minorities to be heard.

The correspondence columns of the *Journal of the American Medical Association* should be a forum where matters of the public relations of medicine, or any other serious medical topic, could be freely discussed. It is my opinion, however, that the *Journal of the American Medical Association* does not serve this function. Apparently, it only gives space to opinions that adhere to the orthodox party line. It cannot tolerate criticism.

It distresses me to see the generally admirable *New England Journal of Medicine* bending in this direction, even if only slightly. I will go along with you that we should get busy at the grass roots, but I depart from you in your taboo of direct approaches at other levels.

If the public discovers that there is a row in the medical profession (they probably have discovered it), I believe this will be to the good. If the public know that the doctors have honest differences of opinion, I believe it is more likely to create confidence than if they look upon us as a great crowd of yes-men. After all, the public are the consumers of medical service, and have as direct an interest in, and as much right to be heard on, the problems of how medical care is to be provided, as the doctors have.

J H MEANS, M D

Boston

NOTE: Dr Means seems to have missed the point of the editorial in question, perhaps being unaware of a current type of criticism, much of it thoughtless, some of it possibly malicious, that has been directed against the American Medical Association since the assessment was announced. This applies to destructive criticism that has served no useful purpose but has, unfortunately, tended to create indecision and distrust.

It is difficult to understand Dr Means's reference to what he considers an apparent attempt on the part of the *Journal* "to shut off efforts at reform by approaches directed at higher levels." Such an accusation appears to be answered in the last paragraph of the editorial to which he takes exception, which specifically states, "If your association in your opinion is at fault then start the correction from within."

It should further be apparent to its readers that the correspondence columns of the *New England Journal of Medicine* are open to all sincere and constructive expressions of opinion, within the limits of its space — that the *Journal* is far from bending in this direction" of giving space only to opinions "that adhere to the orthodox party line."

In short, the *Journal* still maintains its belief that helpful criticism is of great value and that all sides of any controversial subject should be presented, but that little good can come of wholesale condemnation of the one organization that represents the medical fraternity in America. — Ep

CONSTRUCTIVE CRITICISM

To the Editor: In a recent issue of the *Journal* there were a number of letters voicing disapproval of the \$25 00 assessment recently passed by the House of Delegates of the American Medical Association. Some of the criticisms were justified, and some were even quite good. However in none of them were there any constructive suggestions on how better to meet the challenge. Although I am not yet a member of the American Medical Association, I have recently contributed

\$25 00 to this fund, together with my criticisms and suggestions.

It seems to me that the medical profession should have as its goal the improvement of medical care, either qualitative or quantitative, and that its members should be leaders in advocating any change, Government or private, that will improve the quality of medical care, result in better distribution of care or remove the economic hazard from illness without at the same time lowering the quality of the care. The program suggested was as follows:

PRIVATE ACTIVITIES

Expand such voluntary insurance plans as Blue Cross and Blue Shield and follow the suggestions of Dr Hawley to bring nationwide coverage to these plans.

Encourage private insurance plans, even though lay people are on the board of control, sponsored by co-operatives, industries and labor unions.

Introduce more and better public-relations systems, similar to that introduced in Colorado, with some voluntary control of fee schedules, possibly by the publication of average fees. We should tell the people about the cost of medical education and the doctor's overhead expenses.

Encourage better distribution of doctors by more rotating residencies, continued organization of and better hospital facilities for the general practitioner, and encouragement of medical students, by their teachers, to enter practice in rural communities.

GOVERNMENT ACTIVITIES

Improve and increase the public-health facilities by setting up new public-health departments in counties not now having them and expanding the public-health department's educational program.

Federal grants to finance the education of a certain number of medical students, who would agree to practice for five years in a rural community. These grants would be administered by the medical schools.

Federal aid, through the states or private insurance plans, to finance the medical care of the destitute.

A federal program to "stamp out" tuberculosis. This could be done in two distinct parts: mass chest x-ray examination by the public-health department with the aid and co-operation of local medical societies, and federal grants to the states for the construction of a sufficient number of hospitals to take care of all tuberculous patients without a waiting period and additional grants to be used for care of the patients' dependents during the time he is incapacitated by his disease.

Federal aid to the states for the adequate care of mental illnesses to be used for the construction and staffing of adequate hospitals.

Federal aid to the states for the treatment of chronic alcoholism.

It seems to me that such a program would be workable and could be administered effectively and, though expensive, would result in a worth-while improvement of the health of the nation.

J PHILIP AMBUEL, M D

904 Naval Avenue
Bremerton, Washington

THE CARE OF THE SICK

To the Editor: What is the plain nature of the crisis in which American medicine finds itself today? It is the judgment of an increasing number of people in our society that the profession is not fulfilling its ancient function of ministering to the sick as our well remembered fathers did, simply and honestly. It includes a feeling that the magnificent modern developments in the science of medicine do not filter down among the common people except through an increasingly impenetrable screen of high fees and inscrutable specialism at the top, and men of poorer quality in the highways and byways at the bottom where the people see them. In the high towers of the medical centers everyone recognizes that a high quality of medicine can be obtained for a high price and after a long wait, but who will take care of my cold, my measles or my sprained ankle, and do it reliably and well? Why is it that I must take my chances with the optometrist in my small city, or else have to wait six weeks

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RUSSELL S. FISHER, M.D.

Research Fellow, Department of Legal Medicine
Harvard Medical School

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

EMERGENCY MATERNITY AND INFANT CARE PROGRAM

Payment for maternity care and for care of infants under one year of age is still available under this program. However, the Massachusetts Department of Public Health is calling attention to the fact that *no authorization for payment for pediatric care rendered after April 20, 1949*, may be issued under this program.

All bills for medical and hospital care must be submitted before May 1, 1949, to Massachusetts Department of Public Health, Division of Maternal and Child Health, 73 Tremont Street, Boston.

BLUE CROSS-BLUE SHIELD

AMCP PLANS REACH SIXTY

In accepting membership applications in January from Arkansas Medical and Hospital Service, of Little Rock, Central New York Medical Plan, of Syracuse, Klamath Medical Service Bureau, of Klamath Falls, Oregon, Physicians Association of Clackamas County, Oregon City, Oregon (reinstatement), and Puerto Rico Hospital Service Association, of San Juan, Associated Medical Care Plans has increased its membership to a total of sixty plans.

This leaves only three eligible plans in active operation that are not members of AMCP, although others, now in process of organization, may soon become eligible for membership.

MISCELLANY

PHYSICIANS' WELCOME CENTER IN PARIS

Doctors from around the world who arrive in France will find a warm welcome awaiting them at the new center recently opened in Paris at 60 Boulevard de Latour-Maubourg by the French Medical Association. The center plans to give visiting physicians information on all subjects of interest to them, to arrange hospital visits and consultations and to direct attention to various scientific congresses and lectures.

As an added service to the medical profession, the French Medical Association, in conjunction with the Commissariat General au Tourisme, official Government tourist organization, will advise on travel in France and give information on hotels, restaurants, amusements and cultural activities.

The French Medical Association welcome center will be open daily from 9 to 12 and 1 30 to 6.

ARMY MEDICAL CORPS SPECIALISTS

As of January 25, 1949, 143 Regular Army Medical Corps officers and 10 civilian component officers on active duty were certified as diplomates of American Specialty Boards. This represents an increase of 51 from the date of the last published survey (September 1, 1947).

Specialists to fulfill current requirements of the Army are needed in all fields. In the specialty fields of allergy, cardiology, gastroenterology, pulmonary diseases and neurosurgery the Army still does not have a board-certified specialist, although officers are in training in each of these fields to enable them to reach eligibility for board examinations.

Commissions in the Medical Corps, both Regular Army and Reserve, up to and including the rank of lieutenant colonel, are available in these fields for qualified civilian physicians, depending upon length of professional experience and subject to Army regulations.

CORRESPONDENCE

WARNING REGARDING LITHIUM CHLORIDE

To the Editor In view of the recent deaths alleged to have been caused by the use of table-salt substitutes containing lithium chloride, and because of an increasing number of reports from physicians of observance of hitherto unexplained symptoms following administration, it is believed that an EMERGENCY WARNING should be issued to physicians, hospitals and wholesale and retail distributing outlets that products of this nature may cause injury to the users and to suggest that further prescriptions, distribution and sale be discontinued immediately, until further notice.

The United States Food and Drug Administration has taken steps toward the recall from the market of all these preparations. Superintendents of hospitals, and practicing physicians generally, are hereby requested to take the necessary measures to prevent further administration and use of these products.

CARL S. FERGUSON, *Director*

Division of Food and Drugs
Massachusetts Department of Public Health

THE RIGHT TO CRITICIZE

To the Editor Your editorial entitled "This AMA—What is it?" in the February 3 issue of the *Journal*, although it contains some truth that indeed needs saying at this juncture, also, in my opinion, displays some regrettable weaknesses.

The statement that destructive criticism "harms many and helps none" is incomplete and misleading. Destructive criticism may identify evil and pave the way to its correction. It should be followed by constructive criticism, which promotes the development of something good. In any event, we can say that destructive criticism elected Harry Truman. Whether that's for good or bad time will tell.

When you say of the critics within the ranks of medicine, "most of whom believe that they have just complaints, and derive a feeling of pleasure or sense of importance from pro-

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Psychiatry for the Pediatrician. By Hale F. Shirley, M.D., associate professor of pediatrics and psychiatry, and executive director of the Child Psychiatry Unit, Stanford University School of Medicine. 8°, cloth, 442 pp. New York: The Commonwealth Fund, 1948. \$4.50.

This book is the outgrowth of lectures given to medical students of Stanford University Medical School and likewise is a revision and expansion of a syllabus written for the clinical use of students and resident staff members of the Stanford University Hospitals. It is not intended as a complete textbook or scientific treatise, but as an introduction to the subject, and is primarily written for the medical student, the pediatrician and the general practitioner. The text has been written in simple language with emphasis on the problems frequently encountered by the pediatrician in his practice. The material has been well arranged and considers the behavior problems of children in all their aspects. The preliminary chapters discuss child guidance, development and habit training, followed by chapters on physical, intellectual, emotional, sexual and environmental factors and problems. The last two chapters have to do with the investigation and treatment of behavior problems. Lists of selected references are appended to the various chapters. A glossary concludes the text, which is printed with a good type on light, nonglare paper. There is a good index. It is a pleasure to handle this volume. It should be in all medical libraries and prove useful to pediatricians and all persons interested in child guidance.

Hemostatic Agents, with Particular Reference to Thrombin, Fibrinogen and Absorbable Cellulose. By Walter H. Seegers, M.S., Ph.D., professor of physiology, Wayne University College of Medicine, Detroit, and Elwood A. Sharp, M.D., Sc.D., director, Department of Clinical Investigation, Parke, Davis and Company, and lecturer, Department of Medicine, Wayne University College of Medicine, Detroit. 8°, cloth, 131 pp., with 27 illustrations and 9 tables. Springfield, Illinois: Charles C. Thomas, 1948. \$4.50.

This monograph on coagulants is based on developmental work conducted during the past few years by research workers. The literature of the subject is reviewed and analyzed. The bibliography appended to the text comprises 370 references to periodical articles. This valuable monograph should be in all medical libraries and in the collections of all persons interested in coagulants.

The Training of a Doctor. Report of the Medical Curriculum Committee of the British Medical Association. 8°, cloth, 151 pp. London: Butterworth and Company (Publishers), Limited, 1948. 7s. 6d.

This exhaustive report on the medical curriculum in British Universities is detailed in its recommendations. The committee's task was to consider what modifications should be made in the aim, content and structure of the medical curriculum in the light of increasing medical and educational knowledge and of the changing needs of medical practice. The summary lists 211 different recommendations. The report is divided into five parts: preliminary problems, pre-medical education, preclinical period, clinical period, and clinical curriculum. The last part, comprising nearly half the text, discusses in detail all clinical branches of the curriculum, and also includes a timetable or schedule for a seven-year course of instruction from the premedical period to internship, professional examinations and a consideration of the intern year. This valuable report should be in all deans' libraries and medical libraries and is essential to all persons interested in medical education.

Outline of Physiology. By William R. Amberson, Ph.D., professor of physiology, University of Maryland, and Dietrich C. Smith, Ph.D., associate professor of physiology, University

of Maryland. 4°, cloth, 502 pp., with 193 illustrations, by the late Norris Jones, instructor in scientific illustrating, Swarthmore College, and William Loechel. Second edition. Baltimore: Williams and Wilkins Company, 1948. \$5.00.

In this second edition of a work written principally for first-year students, much of the text has been completely rewritten, especially the chapters on the central nervous system, circulation, endocrines and reproduction. Chapters have been added on catalysis and enzymes, vitamins, sensation and the heart. The text is well printed with a good type in a two-column format. The illustrations are excellent. A comprehensive index concludes the volume.

Modern Drugs in General Practice. By Ethel Browning, M.D., Ch.B. 8°, cloth, 223 pp. Second edition. Baltimore: Williams and Wilkins Company, 1947. \$4.00.

In the new edition of this manual for the general practitioner, the author has included penicillin and has amplified the chapter on the sulfonamides. The text has been revised to include the new drugs of recognized merit. There is a chapter on thiouracil and methylthiouracil. Lists of selected references are appended to the chapters. The volume is concluded with a good index. The text was printed in Great Britain, and the publishing is good.

History of Factory and Mine Fatigue. By Ludwig Teleky, M.D. 8°, cloth, 342 pp. New York: Columbia University Press, 1948. \$4.50.

This small volume constitutes an outline of the history of industrial hygiene. The material is well organized, and the text well written. The printing has been done with a good, large type on lightweight, nonglare paper. A bibliography of 33 pages is appended to the text. A comprehensive index concludes the volume. The book is recommended for all medical and public libraries and all persons interested in the subject.

The Healthy Hunzas. By J. I. Rodale, editor of *Organic Gardening*. 8°, cloth, 263 pp., with 16 illustrations and 1 map. Emmaus, Pennsylvania: Rodale Press, 1948. \$2.75.

The Hunzas are a civilized race of people of Northwest India who are remarkably healthy and who have occupied their small domain for hundreds of years, and now number about 22,000. Living on a high plateau near Tibet, they lead a simple and isolated life. They enjoy a low percentage of morbidity. The present volume constitutes a plea for organic fertilization of the soil. The volume is well published and should prove valuable to persons interested in public health and nutrition.

Rural Health and Medical Care. By Frederick D. Mott, M.D., and Milton I. Roemer, M.D., M.P.H. 8°, cloth, 608 pp. New York: McGraw-Hill Book Company, Incorporated, 1948. \$6.50.

This new volume in the field of medical care and services constitutes a comprehensive study of the rural aspects of the subject in the United States. The various chapters discuss present-day levels and trends of rural health, physicians and other health personnel, health facilities, medical service and expenditures in rural areas, governmental services and voluntary health problems. The material is well published in every way and is concluded with a comprehensive subject index. The book is recommended to all medical and public libraries.

Biology of Pathogenic Fungi. Edited by Walter J. Nickerson, Ph.D., assistant professor of botany, Wheaton College, and lecturer in medical mycology and dermatology, Tufts College Medical School. With a foreword by J. G. Hopkins, M.D., professor of dermatology, Columbia University College of Physicians and Surgeons. 8°, cloth, 236 pp., with 47 illustrations and plates and 52 tables. Waltham, Massachusetts: Chronica Botanica Company, New York City: Stechert-Hafner, Incorporated, 1947. \$5.00.

This volume is the joint work of a number of authors and discusses some aspects of the biology, physiology and biochemistry of the fungi pathogenic to man. Extensive indexes of authors and subjects conclude the volume. The text is printed with a good type on nonglare paper. The volume is recommended for all medical, public-health and scientific libraries.

for an appointment to have my glasses checked in the big city by the great eye specialist?

Why has all this come about? I think it is partly because of a certain paranoid pride among the profession in the great teaching centers. Perfectionism has reached such a point in the great medical schools that courses on the care of the patient are a joke, a minor elective. Medical students, professors and even the great clinics are so swallowed up in the pride of scientific achievement that the patient, who should be the heart and core of medicine, has been lost somewhere among the laboratories. Give him a rarity like thrombocytopenic purpura or Addison's disease, and he becomes a distinguished medical problem, but let him have cerumen in his ears or a tonsillitis and he is scarcely worthy of the attention of the meanest medical student, or perhaps even of a technician. This attitude is sedulously drilled into the student from his first flights in anatomy until he emerges from his big-shot residency and hangs out his shingle. For eight or nine years he has studied rare diseases and excelled in solving diagnostic traps invented by his specialist instructors. Then what happens?

One of two things happens. If he has carefully played his cards, an assistantship is awaiting him right in the medical center, where he can continue his monasticism, never have to become a citizen at large, and live the rest of his life an approved monk of the inner fraternity, teaching the gospel of high-priest specialism to new generations of admiring students so that they will follow his lead. Or he may fail in his economic safeguards and have to get out into a community and scratch himself out a practice. In the jargon of the great medical center that constitutes failure. Yet always a majority of the graduates of the great schools do this. They work like beavers. They find that they have to unlearn their training, start with their discovery of the human beings they are meeting for the first time in homes and community affairs, and take care, not of rarities, but of their prevalent ailments. Nobody at the school bothered to teach much about these problems — how to handle the high-school quarterback with the sprained knee, how to console the old lady with a hemiplegia, how to command the obedient co-operation of the business man with a coronary thrombosis. These patients cannot be cured with an x-ray film or an electrocardiogram. What is to be done for the patient with rheumatoid arthritis who cannot afford a hospital? What about the cancer patient whom the surgeons have given up? How does one get care for the senile dementia, the houseful of scarlet fever or the four healthy children of the widow with virus pneumonia? Are these not problems worthy of the best medical judgment? Yet where in our professional system is the provision for care of these problems by first-rate talent?

There are plenty of graduates of substandard schools in the neighborhood, but where are the good men who will go out at night on an emergency? In many a community they are lacking. Men who should be there are sweating out their slow climb up the crowded ladder in the big city. And even there their eyes are so glued on the grinding competition of a specialty that they cannot see the crying need of good general practitioners in the city all around them. Who takes care of whooping cough, Colles fractures and epidemic diarrheas in the big city — the pediatrician, the orthopedic surgeon, and the specialist in internal medicine? At times, yes, or perhaps the hotel doctor in the next block. But where is the family physician? In many cases he just isn't.

If the increasing demand of the American people for better distributed medical service finally produces socialized medicine, it will be because the profession has as yet made insufficient provision in its training program for the unceasing production of good family physicians. It is perfectly true that no one man can learn everything a good general practitioner needs to know. But some of our great teaching centers have stopped trying to tackle the problem. They have insidiously allowed their faculties to be monopolized by full-time research specialists who belittle the LMD. The entire atmosphere of the great schools and hospitals covertly points up the errors and inadequacies of the general practitioner, even though it has been a family doctor who diagnosed the need for consultation in nearly every hospital case the students see. Little do they realize how many of them later will themselves be the LMD. What is needed is a department of general practice in the medical schools, taught by suburban practitioners who bring the community viewpoint into

the classroom. For such teaching no large-city physician is qualified. The problem of medical care in the smaller community is outside the comprehension of the institutionalized specialist. The whole problem of prodromal symptoms and the early, uncertain pictures of the prediagnostic stages of common diseases is badly taught in large hospitals. The common maintenance therapeutic procedures of office or industrial practice are likewise poorly presented in the usual medical curriculum. Matters of social service, public-health facilities and liaison with charities and state or county facilities are ignored. And such viewpoints as the doctor's position and responsibilities as a citizen in the community are left untouched. These should be integral parts of the general practitioner's training. All physicians, of whatever specialty, should be familiar with them. A course in general practice should be required of all medical students, if only to emphasize the type of liaison necessary between family doctor and specialist. Specialists need to learn how often their care of the patient fails because of the lack of any instructions for follow-up study addressed either to the family physician or to the patient. Both groups need to know the vast difference in facilities between city office and country office and between home and hospital.

If socialized medicine comes, it will be partly at least because this job has not been done. When will the medical centers learn, as the medical societies are learning, that the backbone of American medicine is not in medical schools and hospitals but rather in communities, homes and offices all over the land? The real ambassador of American medicine to the people is not the public-relations expert of the large hospital, but rather the family doctor in thousands of villages and cities. And this the professors must learn if the profession is to maintain its place in the American system.

HENRY F. HOWE, M.D.

Cohasset, Massachusetts

BOOK REVIEWS

Medical Writing: The Technique and the Art Morris Fishbein, M.D. With the assistance of Jewel F. Whelan. Second edition. 8°, cloth, 292 pp., with 36 illustrations. Philadelphia: The Blakiston Company, 1948. \$4.00.

The first edition of this small book was published in 1938. In this new edition an extensive revision has been based upon the handling of thousands of manuscripts for the *Journal of the American Medical Association* and the special periodicals of the Association. A very valuable chapter comprises the standard abbreviations for periodicals and serials listed, as well as an additional list of periodicals not now listed, in the *Quarterly Cumulative Index Medicus*. These lists are invaluable to medical librarians and all persons interested in the writing of medical papers. The list of recognized forms for eponymic diseases is likewise very important. It is taken from the standard nomenclature of the Association. The material is well arranged and covers the whole field of medical writing from the selection of the topic to the finished printed product. The publishing is excellent in every way. The volume should be in all medical libraries and should be accessible to all persons writing medical papers.

Germicides, Antiseptics and Disinfectants for Hospital Use By Dewey H. Palmer. Paper. 15 pp. New York: Hospital Bureau of Standards and Supplies, Incorporated, 1948. \$1.00.

The service a patient receives in a hospital is the result of collaboration of many individuals. Such collaboration is easiest when there is a recognized hospital practice to serve as a basis for performance. This recent publication delineates the basis for choosing germicides, antiseptics and disinfectants and outlines techniques for their use. The contribution is noteworthy in that it represents the first attempt to provide an authoritative consensus on the relative merits of chemical disinfectants and special recommendations for hospital practice in this controversial field. In accomplishing this purpose, it inevitably focuses attention on the need for continuing investigation of the broad problem of detergents and germicides.

trations and 7 color plates St. Louis C V Mosby Company, 1948 \$5.50

This synopsis was written principally for medical students. The text covers briefly the whole field of ophthalmology. The printing is well done with a large type, and the illustrations and color plates are excellent. A good index completes the volume. The manual should prove useful to its intended clientele.

Arterial Hypertension. By David Ayman, M.D., instructor in medicine, Tufts College Medical School, associate visiting physician and head of out-patient clinic in hypertension, Beth Israel Hospital, Boston. Reprinted from *Oxford Loose-Leaf Medicine* with the same pagination. 8°, cloth, pp 508 (173-265) with 9 charts. New York: Oxford University Press, 1948. \$2.50.

This monograph on arterial hypertension, written by a specialist on the subject, emphasizes methods of treatment. A bibliography of ninety-nine references concludes the text. The volume is well published and should prove valuable to physicians interested in the subject.

NOTICES

ANNOUNCEMENT

Dr. B. W. Mandelstam has left his position as assistant director at the Beth Israel Hospital, Boston, to assume that of executive director at the Nathan Littauer Hospital, Gloversville, New York.

NEW ENGLAND CENTER HOSPITAL (JOSEPH H. PRATT DIAGNOSTIC HOSPITAL)

30 Bennet Street, Boston
Lecture Hall, 9-10 a.m.

MEDICAL CONFERENCE PROGRAM

- Friday, March 4 Mechanism of Blood Destruction in Congenital Hemolytic Jaundice. Drs. Charles P. Emerson, Jr., Shu Chu Shen, William B. Castle and Thomas Hale Ham (to be given by Dr. Ham).
Wednesday, March 9 Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon.
Friday, March 11 Some New Methods for the Histochemical Demonstration of Enzymes and Compounds with Active Carbonyl Groups. Dr. Arnold N. Seligman.
Tuesday, March 15 Journal Review.
Friday, March 18 The Role of Mitochondria in Cellular Metabolism. Dr. William F. Loomis.
Tuesday, March 22 Surgical Emergencies in the New-Born. Dr. Lorye E. Hackworth.
Friday, March 25 Artificial Kidney. Dr. John M. Merrill.

From 9 to 10 a.m. on Wednesday (except the second Wednesday), Thursday and Saturday mornings clinics will be given by members of the hospital staff. Medical rounds are conducted each weekday except Saturday by members of the hospital staff from 12 to 1 p.m. On the second and fourth Fridays of the month, March 11 and 25 Therapeutic Conferences will be held with round-table discussion from 2 to 4 p.m., with Dr. Robert P. McCombs as moderator. On the second and fourth Fridays, March 11 and 25 Dr. Merrill Sosman will conduct X-Ray Conferences from 4 to 6 p.m.

All exercises are open to the medical profession.

GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium, Boston University School of Medicine, 80 East Concord Street, Boston, on Wednesday, March 16, at 8:15 p.m. A symposium entitled "Vertigo and Simulative Symptoms" will be presented from the combined points of view of the anatomist, otologist, internist and neurosurgeon. The chairman will be Dr. Philip E. Meltzer, and the speakers

will be Dr. Miles Atkinson, of New York City, and Drs. Benjamin Spector and William H. Sweet.

NORFOLK DISTRICT MEDICAL SOCIETY

A meeting of the Norfolk District Medical Society will be held at the Boston Medical Library, 8 Fenway, Boston (Telephone Commonwealth 6-2800), on Tuesday, March 22, at 8 p.m.

The following scientific program, entitled "Symposium on Care of Advanced Cancer," will be presented:

Super-Radical Treatment. Ernest M. Daland, M.D.
Radiological Aspects. Joseph H. Marks, M.D.
Hormonal Aspects. Ira T. Nathanson, M.D.
Chemotherapeutic Aspects. Sidney Farber, M.D.

All physicians are invited.

NORFOLK DISTRICT WOMAN'S AUXILIARY

The Woman's Auxiliary of the Norfolk District Medical Society will meet in the State Suite at the Copley Plaza Hotel, Boston, on Tuesday, March 29, at 2:30 p.m. Mrs. Dorothy Hayward, R.N., assistant executive secretary, Health and Hospital Division, Greater Boston Community Council, will speak on the subject "Nursing in the Future."

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

The Committee on Education of the New England Society of Anesthesiologists plans to hold all-day, Saturday, clinics primarily for the physician practicing part-time anesthesia.

On Saturday, April 2, at the Rhode Island Hospital, Providence, Rhode Island, under the direction of Dr. Meyer Saklad. The morning session is devoted to clinical demonstrations and starts promptly at 8 o'clock. The afternoon session will be devoted to "Anoxia and Inhalation Therapy."

On Saturday, May 7, at the St. Francis Hospital, Hartford, Connecticut, under the direction of Dr. Stevens J. Martin. The morning session starts at 8 o'clock and is devoted to operative clinics; lectures will be held in the afternoon.

Any physician may attend by making reservations in writing to the respective directors. It is requested that reservations be made early.

PHI DELTA EPSILON LECTURE

The third annual Phi Delta Epsilon lecture, entitled "The Future Diabetic," will be delivered by Dr. Elliott P. Joslin at the Hahnemann Medical College, Philadelphia, on April 4.

All physicians, medical students and interested persons are invited.

WOMAN'S AUXILIARY, SUFFOLK DISTRICT

The Woman's Auxiliary of the Suffolk District Medical Society will hold its annual meeting and election of officers on Thursday, April 7, at 2:30 p.m. in Sprague Hall of the Boston Medical Library, 8 Fenway.

ASSOCIATION FOR PHYSICAL AND MENTAL REHABILITATION

The Association for Physical and Mental Rehabilitation will hold its third annual convention at the Hotel New Yorker, New York City, May 18-21. More than 500 representatives from the nation's Veterans Administration, Army, Navy and Civilian Rehabilitation Agencies will be present. Mr. Leo Berner, chief corrective therapist of the Bronx Veterans Hospital, is chairman for the convention.

Further information may be obtained from H. S. Wettstein, at the Corrective Therapy Section, Veterans Administration Hospital, Bronx, New York.

Failures in Psychiatric Treatment Edited by Paul H Hoch, M.D., New York State Psychiatric Institute, New York City, principal research scientist (psychiatry), New York State Psychiatric Institute, and associate in psychiatry, Columbia University College of Physicians and Surgeons, New York City (The *Proceedings* of the thirty-seventh annual meeting of the American Psychopathological Association, held in New York City, June 1947) 8°, cloth, 241 pp., with illustrations New York Grune & Stratton, 1948 \$4.50

This symposium comprises the *Proceedings* of the annual meeting of the American Psychopathological Association, held in 1947, and contains fifteen papers read at the meeting. The text is concluded with a summary of the symposium findings by the editor. The book is well published, except that a coated paper has been used unnecessarily. The volume is recommended for all medical libraries.

Pathology of Tumours By R. A. Willis, D.Sc., M.D., F.R.C.P., Sir William H. Collins Professor of Human and Comparative Pathology, Royal College of Surgeons, London 8°, cloth, 992 pp., with 500 illustrations London Butterworth and Company (Publishers), Limited, 1948 \$20.00

Dr. Willis has based his text largely on work done in the pathology laboratories of the Alfred Hospital, Melbourne, Australia, between the years 1930 and 1945. The volume is a personal treatise using the author's own observations and conclusions as fully as possible. Similarly, the illustrations, with a few exceptions of photomicrographs, are from personally studied material, and most of the illustrations have not previously been published. The depiction of well known appearances of common tumors has been omitted intentionally, and the less familiar and special features and the range of structure possible in the less common kinds of tumors have been shown; illustrations have not been repeated under different organs or structures. The text is divided into two parts. The first discusses classification and pathology in general. The second is devoted to descriptions of special tumors classified by organ or structure, followed by the tumors of general distribution, teratomas and chorionepitheliomas. Lists of selected references are appended to the various chapters. A comprehensive index concludes the volume. The type, printing and illustrations are excellent. The book was printed and bound in Great Britain and has an added American imprint. The treatise was written primarily for pathologists, research workers and senior medical students. It should be in all medical libraries and should be of interest to pathologists.

Vascular Diseases in Clinical Practice By Irving Wright, M.D., associate professor of clinical medicine, Cornell University Medical College, and chief, Section on Vascular Diseases, Department of Medicine, New York Hospital 8°, cloth, 514 pp., with 104 illustrations Chicago The Year Book Publishers, Incorporated, 1948 \$7.50

This volume is one of the *General Practice Manuals* intended for the general practitioner. The first and second chapters discuss classification and methods of study of the patient. The following chapters are devoted to the different diseases of the vascular system. There is a chapter on industrial and medicolegal medicine in relation to peripheral vascular disease and injury, and an appendix on a method for determining plasma prothrombin. The material is well organized, and the text well written. Lists of pertinent references are appended to the chapters. The type and printing are good, but the coated paper is too heavy for the size of the volume. The manual should prove useful to the practicing physician.

Hutchinson's Food and the Principles of Dietetics Revised by V. H. Mottram, M.A. (Cant.), and George Graham, M.D. (Cant.), F.R.C.P. (Lond.), consulting physician to St. Bartholomew's Hospital 8°, cloth, 727 pp., with 28 illustrations Tenth edition Baltimore Williams and Wilkins Company, 1948 \$6.25

This standard treatise has been thoroughly revised. Much of the text has been rewritten, especially the first part, on

diet in normal life, which is practically new. The text is printed on a light paper with good type. There is a good index. The printing was done in Great Britain. The volume should be in all medical libraries.

Gynaecological and Obstetrical Anatomy By C. F. V. Stout, M.D., M.R.C.S., assistant professor, Department of Anatomy, and sub-dean and tutor, Faculty of Medicine, University of Birmingham. With chapters on the histology of the female reproductive tract and its endocrine control, by F. Jacoby, M.D., Ph.D., lecturer in history, department of anatomy, University College, Cardiff 8°, cloth, 248 pp., with 185 illustrations Baltimore Williams and Wilkins Company, 1948 \$11.00

The first edition of this book was published under the title of *The Anatomy of the Female Pelvis*. In this new edition the title has been changed to cover the new subject matter on the placenta and the anatomy of the fetus in its relation to childbirth. Large parts of the text have been entirely rewritten, and much material and many illustrations have been added. The various types of pelvis have been classified and described. Lists of selected references are appended to the chapters. There is a good index. The type and printing are good, and the color plates are excellent. The printing was done in Great Britain. The price is high for the size of the volume, although the color work must have been expensive. The work should be available to gynecologists and obstetricians. It should be in large medical libraries.

Handbook of Practical Bacteriology: A guide to bacteriological laboratory work By T. J. Mackie, C.B.E., M.D., LL.D., D.P.H., professor of bacteriology, University of Edinburgh, and director of bacteriologic services, City of Edinburgh, and J. E. McCartney, M.D., D.Sc., director of research and pathological services, London County Council 8°, cloth, 624 pp. Eighth edition Baltimore Williams and Wilkins Company, 1948 \$7.00

This standard English handbook of bacteriology has been completely revised and brought up to date. The data formerly published as an appendix to the war editions have been incorporated in the appropriate chapters. The material is well organized, and the text is well written. The publishing is excellent. The volume should prove useful as a guide to its subject.

Essentials of Public Health By William P. Shepard, M.D., M.A. With the collaboration of Charles E. Smith, M.D., D.P.H., Rodney R. Beard, M.D., M.P.H., and Leon B. Reynolds, Sc.D. With a foreword by Ray L. Wilbur, M.D., LL.D. and Sc.D., chancellor, Stanford University 12°, cloth, 600 pp., with 29 charts Philadelphia J. B. Lippincott Company, 1948 \$5.00

This volume constitutes a condensed handbook for the physician and medical student and other persons interested in public health. The subjects of tropical diseases and the public-health aspects of medical care are omitted from the manual. The text is based on the experience of the authors in teaching together for many years. A list of selected references is appended to each chapter. The volume is well published and should prove useful as a compendium on the subject.

Twentieth Century Speech and Voice Correction Edited by Emil Froeschels, M.D., president, International Society for Logopedics and Phoniatrics, and president, New York Society of Speech and Voice Therapy 8°, cloth, 321 pp. New York Philosophical Library, 1948 \$6.00

This work is the joint effort of nineteen specialists in various fields. The text reflects the latest developments in the subject of speech and voice correction. To each chapter is appended a selected list of references. The text is well printed with a good type on a soft nonglare paper. The volume is recommended as a reference source to all interested persons.

Handbook of Ophthalmology By Everett L. Goar, M.D., professor of ophthalmology, Baylor University College of Medicine, Houston, Texas 8°, cloth, 166 pp., with 45 illus

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PROTHROMBIN A CRITIQUE OF METHODS FOR ITS DETERMINATION AND THEIR CLINICAL SIGNIFICANCE*

BENJAMIN ALEXANDER, M.D.,† ANDRE DE VRIES, M.D.,‡ AND ROBERT GOLDSTEIN, M.D.§

BOSTON

AS A result of the widespread use of dicumarol in the prevention and treatment of thromboembolism, clinicians have become increasingly interested in the role of prothrombin in blood coagulation. Investigators are aware that present technics for prothrombin estimation have their limitations. Failure to recognize them may prevent accurate diagnosis, obstruct effective therapy or even invite disaster. It is the purpose of this paper to delineate these limitations and to scrutinize current analytical procedures in the light of recent advances in knowledge of blood coagulation.

GENERAL CONSIDERATIONS

By chemical isolation and purification Seegers et al.¹ have defined the plasma protein component that is convertible to thrombin—namely, prothrombin. Until some other distinguishing physiological or biochemical property is found, determination of prothrombin must involve its conversion to thrombin, which is assayed by its ability to clot fibrinogen.

Recently, plasma factors have been reported that affect the conversion of prothrombin to thrombin by thromboplastin plus calcium.²⁻⁶ Just how they act is not clear, but it is probable that they accelerate, activate or otherwise act as ancillary agents in thrombin evolution. In any event their relation to the conversion of prothrombin to thrombin must be considered in the determination of prothrombin.

At present, no method of measuring prothrombin can assure adequate control of the nonprothrombin variables. Under such circumstances prothrombin values obtained by the generally accepted procedures are the result of several interrelated factors, of which only one is prothrombin. Accordingly, such

values express only "prothrombic activity"¶ instead of "amounts of prothrombin."

Most of the current analytical technics are based upon two methods: the one-stage procedure of Quick⁷ and the two-stage method of Warner et al.^{8||} In Quick's method the clotting time of the plasma is measured after optimal amounts of thromboplastin and calcium are provided. This, the prothrombin time, is the minimal interval that elapses before a macroscopic clot results from the conversion of prothrombin to thrombin. It reflects the amount of thrombin evolved together with the velocity of its evolution. The validity of the method rests upon the assumption that the velocity of prothrombin conversion to thrombin, as well as the latter's coagulation of fibrinogen, is a measure *solely* of prothrombin concentration.

In the two-stage procedure, prothrombin is presumably converted completely to thrombin in defibrinated and diluted plasma. By trial and error a suitable dilution is made that will yield a given amount of thrombin, as measured by its ability to clot a standard fibrinogen solution. Theoretically, sufficient time is allowed to complete prothrombin conversion, obviating possible variations in the velocity of this reaction. Prothrombin is thus measured by the amount, not by the velocity, of thrombin formation.

Frequently, the results obtained by both methods agree closely. Sometimes, however, there is considerable (as much as 100 per cent) discordance between the results—for example, in different species, in infants and in aged plasma, dicumarolized blood and hemophilic serum. Until these discrepancies are satisfactorily explained, results obtained by either method must be interpreted cautiously.

ONE-STAGE METHOD

General Procedure

Oxalated plasma is added to potent thromboplastin extract, the mixture is brought to 37°C,

*We consider this term necessary to distinguish between the amount of prothrombin and such and the activity of a given biologic mixture in the production of thrombin for converting fibrinogen to fibrin.

||We have not included the method of Shonheyder⁹ which is based upon the inverse relation between prothrombin concentration and the amount of thromboplastin required to clot plasma in one hundred and eighty seconds.

*From the Medical Research Laboratory, Beth Israel Hospital and the Department of Medicine, Harvard Medical School. Supported by a grant from the Commonwealth Fund.

†Associate in medicine, Harvard Medical School; visiting physician and associate in medical research, Beth Israel Hospital.

‡Research fellow in medicine, Beth Israel Hospital; formerly fellow, the Rothschild Hadassah University Hospital, Jerusalem, Palestine.

§Assistant in medicine, Harvard Medical School; associate in medicine, Beth Israel Hospital.

MASSACHUSETTS PHYSICIANS ART ASSOCIATION

The Massachusetts Physicians Art Association will hold its annual exhibit in conjunction with the annual meeting of the Massachusetts Medical Society at Worcester, May 24-26. This exhibit includes oil and water-color paintings, drawings, etchings, photographs, carving, sculpture and any other original decorative handiwork done by members. Any member of the Massachusetts Medical Society is eligible for membership and may exhibit this year on payment of \$2.00 annual dues to Dr. Robert Buck, 5 Bay State Road, Boston, treasurer. Nothing will be accepted for the exhibit after May 1. Members will receive further details concerning final arrangements later.

REGULAR CORPS EXAMINATION FOR MEDICAL OFFICERS IN UNITED STATES PUBLIC HEALTH SERVICE

A competitive examination for appointment of medical officers in the Regular Corps of the United States Public Health Service will be held on May 3, 4, and 5, 1949. Appointments, which will be made in the grades of assistant surgeon (first lieutenant) and senior assistant surgeon (captain), are permanent and provide opportunities to qualified physicians for a lifetime career in clinical medicine, research and public health.

As requirements for appointment in the grade of assistant surgeon, the applicant must be a citizen of the United States, at least twenty-one years of age and a graduate of a recognized school of medicine. Physicians now serving internships, who are successful on the examination, will not be placed on active duty in the Regular Corps until completion of internship. Applicants for appointment in the grade of senior assistant surgeon, in addition to the above requirements, must have a total of at least ten years of educational training and professional experience subsequent to high school. (All commissioned officers are appointed to the general service and are subject to change of station.) Qualifying applicants will receive written professional tests, an oral interview, and a physical examination.

Application forms and additional information may be obtained from Surgeon General, United States Public Health Service, Washington 25, D. C. (Attention: Division of Commissioned Officers). Complete applications must be received by April 4, 1949.

SOCIETY MEETINGS AND CONFERENCES

JANUARY 7-APRIL 13 American College of Surgeons Sectional Meetings Page xi issue of December 23

MARCH 2-28 Consultation Clinics for Crippled Children in Massachusetts Page 317 issue of February 24

MARCH 4-25 New England Center Hospital (Joseph H. Pratt Diagnostic Hospital) Medical Conference Program Page 401

MARCH 15 South End Medical Club Page 356 issue of March 3

MARCH 16 Greater Boston Medical Society Page 401

MARCH 22 Norfolk District Medical Society Page 401

MARCH 24 Cornell Medical Alumni Association Page 276, issue of February 17

MARCH 28-APRIL 1 American College of Physicians Page 158 issue of July 22

MARCH 29 Norfolk District Woman's Auxiliary Page 401

APRIL 2 American Academy of Pediatrics Page 318 issue of February 24

APRIL 2 New England Society of Anesthesiologists Page 401

APRIL 2-9 American Association of Industrial Physicians and Surgeons Page 356 issue of March 3

APRIL 4 Phi Delta Epsilon Lecture Page 401

APRIL 5-8 Postgraduate Institute of Philadelphia County Medical Society Page 240 issue of February 10

APRIL 7 Woman's Auxiliary Suffolk District Page 401

APRIL 14 Practical Aspects of the Treatment of Hypertension Dr. John C. Leonard Pentucket Association of Physicians 8:30 p.m. Haverhill

APRIL 14-17 American College of Allergists Page 276 issue of February 17

MAY 4 New England Obstetrical and Gynecological Society Springfield Country Club Springfield

MAY 5 Suffolk Censors' Meeting Page 276, issue of February 17

MAY 7 New England Society of Anesthesiologists Page 401

MAY 16-19 American Urological Association Elton Hotel, Los Angeles California

MAY 18-21 Association for Physical and Mental Rehabilitation Memorial Auditorium, Worcester

MAY 24-26 Massachusetts Medical Society Annual Meeting, Worcester

MAY 24-26 Massachusetts Physicians Art Association, Worcester

MAY 26-28 American Goutier Association, Hotel Lorraine, Madison, Wisconsin

MAY 30-JUNE 3 International Congress on Rheumatic Diseases, 800 issue of November 18

JUNE 20-23 Annual Conference of Health Officers and Public Health Nurses Page xviii, issue of February 3

SEPTEMBER 28-30 Mississippi Valley Medical Society Page 159 issue of December 30

NOVEMBER 2 New England Obstetrical and Gynecological Society, Hotel Somerset Boston

DISTRICT MEDICAL SOCIETIES

HAMPDEN

APRIL 26 6:00 p.m. Hotel Highland, Springfield (Deaf and Convulsive Disorders) Dr. Douglas T. Davidson

HAMPSHIRE

MAY 4 Annual Meeting and Election of Officers

MIDDLESEX EAST

MARCH 23

MAY 11

MIDDLESEX SOUTH

APRIL 20 Annual Meeting Hotel Continental Cambridge

NORFOLK

MARCH 22

MARCH 29 Woman's Auxiliary

SUFFOLK

APRIL 7 Woman's Auxiliary

MAY 3 Censors' Meeting

WORCESTER NORTH

APRIL 27 Annual Meeting

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MARCH 17

FRIDAY MARCH 18

*9:00-10:00 a.m. The Role of Mitochondria in Cellular Metabolism Dr. William F. Loomis New England Center Hospital (Joseph H. Pratt Diagnostic Hospital)

*9:00 a.m.-12:00 m. Combined Medical and Surgical Staff Conference Peter Bent Brigham Hospital

*12:00 m. X-Ray Conference Margaret Jewett Hall, Mt. Auburn Hospital, Cambridge

*1:30 p.m. Tumor Clinic Out Patient Department, Mt. Auburn Hospital, Cambridge

MONDAY MARCH 21

*12:15-1:15 p.m. Clinicopathological Conference. Mount Auburn Hospital Peter Bent Brigham Hospital

TUESDAY MARCH 22

*9:00-10:00 a.m. Surgical Emergencies in the New Born Dr. Joseph E. Hackworth New England Center Hospital (Joseph H. Pratt Diagnostic Hospital)

*12:15-1:15 p.m. Clinicoradiological Conference Peter Bent Brigham Hospital

*1:30-2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

*7:00 p.m. Physiology and Pathology of the Kidney Dr. Peter Van Slyke House Officers' Association New Chester Hotel, theater Dowling Building Boston City Hospital.

*8:00 p.m. Norfolk District Medical Society Boston Library 8 Fenway

WEDNESDAY MARCH 23

*11:00 a.m.-12:00 m. Medical Rounds. Amphytheater Children's Hospital

*12:00 m.-1:00 p.m. Clinicopathological Conference Peter Bent Brigham Hospital Amphytheater

*2:00-3:00 p.m. Combined Clinic by the Medical, Surgical, and Orthopedic Services Amphytheater Children's Hospital

*Open to the medical profession

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PROTHROMBIN: A CRITIQUE OF METHODS FOR ITS DETERMINATION AND THEIR CLINICAL SIGNIFICANCE*

BENJAMIN ALEXANDER, M.D.,† ANDRE DE VRIES, M.D.,‡ AND ROBERT GOLDSTEIN, M.D.§

BOSTON

AS a result of the widespread use of dicumarol in the prevention and treatment of thromboclosism, clinicians have become increasingly interested in the role of prothrombin in blood coagulation. Investigators are aware that present techniques of prothrombin estimation have their limitations and that failure to recognize them may prevent accurate diagnosis, obstruct effective therapy, or even invite disaster. It is the purpose of this paper to delineate these limitations and to scrutinize current analytical procedures in the light of recent advances in knowledge of blood coagulation.

GENERAL CONSIDERATIONS

By chemical isolation and purification Seegers and his associates¹ have defined the plasma protein component that is convertible to thrombin—namely, prothrombin. Until some other distinguishing physiological or biochemical property is found, determination of prothrombin must involve its conversion to thrombin, which is assayed by its ability to clot fibrinogen.

Recently, plasma factors have been reported that affect the conversion of prothrombin to thrombin in the presence of thromboplastin plus calcium.²⁻⁶ Just how they act is not clear, but it is probable that they accelerate, activate, or otherwise act as ancillary agents in thrombin evolution. In any event, their action on the conversion of prothrombin to thrombin must be considered in the determination of prothrombin.

At present, no method of measuring prothrombin can assure adequate control of the nonprothrombin variables. Under such circumstances, prothrombin values obtained by the generally accepted procedures are the result of several interrelated factors, of which only one is prothrombin. Accordingly, such

values express only "prothrombic activity"⁶ instead of "amounts of prothrombin."

Most of the current analytical techniques are based upon two methods: the one-stage procedure of Quick⁷ and the two-stage method of Warner et al.⁸ In Quick's method, the clotting time of the plasma is measured after optimal amounts of thromboplastin and calcium are provided. This, the prothrombin time, is the minimal interval that elapses before a macroscopic clot results from the conversion of prothrombin to thrombin. It reflects the amount of thrombin evolved together with the velocity of its evolution. The validity of the method rests upon the assumption that the velocity of prothrombin conversion to thrombin, as well as the latter's coagulation of fibrinogen, is a measure solely of prothrombin concentration.

In the two-stage procedure, prothrombin is presumably converted completely to thrombin in defibrinated and diluted plasma. By trial and error a suitable dilution is made that will yield a given amount of thrombin, as measured by its ability to clot a standard fibrinogen solution. Theoretically, sufficient time is allowed to complete prothrombin conversion, obviating possible variations in the velocity of this reaction. Prothrombin is thus measured by the amount, not by the velocity of thrombin formation.

Frequently, the results obtained by both methods agree closely. Sometimes, however, there is considerable (as much as 100 per cent) discordance between the results—for example, in different species, in infants and in aged plasma, dicumarolized blood, and hemophilic serum. Until these discrepancies are satisfactorily explained, results obtained by either method must be interpreted cautiously.

ONE-STAGE METHOD

General Procedure

Oxalated plasma is added to potent thromboplastin extract; the mixture is brought to 37°C,

*We consider this term necessary to distinguish between the amount of prothrombin as such and the activity of a given biologic mixture in the production of thrombin from converting fibrinogen to fibrin.

†We have not included the method of Shonheyder,⁹ which is based upon the inverse relation between prothrombin concentration and the amount of thrombin required to clot plasma in one hundred and eighty seconds.

From the Medical Research Laboratory, Beth Israel Hospital, and Department of Medicine, Harvard Medical School, supported by a grant from the Commonwealth Fund.

Associate in medicine, Harvard Medical School, visiting physician and associate in medical research, Beth Israel Hospital.

Research fellow in medicine, Beth Israel Hospital, formerly fellow, Rothschild Hadassah University Hospital, Jerusalem, Palestine.

Assistant in medicine, Harvard Medical School, associate in medicine, Beth Israel Hospital.

and calcium chloride solution added From this instant the time required for clotting (the prothrombin time) is measured

Serum prothrombin is similarly determined except that fibrinogen must also be provided

Certain Clotting Components

Fibrinogen The clinical and experimental value of the one-stage method needs no elaboration Nevertheless, it suffers from several limitations For example, afibrinogenemic blood containing normal amounts of prothrombin will show an infinitely prolonged prothrombin time, which would be interpreted as indicating zero prothrombin The addition of fibrinogen rectifies this defect The relation between fibrinogen concentration and prothrombic

The reactivity of fibrinogen to thrombin differs also from one species to another¹⁴ This must be duly considered when apparent prothrombin concentration of one species is compared with that of another

Labile factor As plasma ages its prothrombin time increases, and yet its prothrombin concentration, as determined by the two-stage technic or by chemical isolation, may be normal¹⁵ The decrease in prothrombic activity is due to deterioration of a labile component found in fresh plasma,* which is necessary for the rapid conversion of prothrombin to thrombin² This factor, more labile at refrigerator or body temperature than prothrombin, is not fibrinogen, and is not appreciably adsorbed by barium sulfate, in contradistinction to prothrombin¹¹

No case of deficiency of labile factor has been recorded Two subjects in whom the elevated prothrombin time seemed due, at least in part, to low concentrations of labile factor were observed The plasma of Subject 1, who had extensive hepatic damage from obstructive jaundice with a malignant tumor involving the liver, showed much less prothrombic activity by the orthodox one-stage technic than when the determination was made on a mixture of his plasma with normal plasma rendered prothrombin free by adsorption with barium sulfate (Table 2), as pointed out below Furthermore, the

TABLE 1 Relation between Plasma Fibrinogen Concentration and Prothrombic Activity

PLASMA MIXTURE		FIBRINOGEN CONCENTRA- TION	PROTHROMBIC ACTIVITY	
Experiment 1*			TIME	CONCEN- TRATION
PARTS OF AFIBRINO- GENEMIC	PARTS OF NORMAL	mg per 100 cc	sec	%
0	1	250	13 0	100
1 0	3	188	12 5	100
1 0	1	125	12 8	100
2 3	1	76	14 7	40
4 0	1	50	16 5	25
9 0	1	25	22 2	11
Experiment 2†				
0	1	171 0	13 7	100
3 0	7	120 0	13 2	100
5 0	5	86 0	13 3	100
6 0	4	68 0	14 2	46
7 0	3	51 0	14 4	43
8 0	2	34 0	16 5	25
9 0	1	17 0	22 8	10
19 0	1	8 5	45 0	4

*Normal plasma mixed with plasma from subject with congenital afibrinogenemia

†Normal plasma mixed with normal plasma rendered fibrinogen free by addition of thrombin (5 units to 1 cc of plasma)

activity is shown in Table 1 Since hypofibrinogenemic plasma may exhibit decreased prothrombic activity despite normal prothrombin content, an elevated prothrombin time must be interpreted cautiously in those conditions in which fibrinopenia as well as hypoprothrombinemia may occur (such as liver disease)

The quality of fibrinogen and the milieu in which it is dissolved are also important We have observed that as plasma ages, it clots less readily on the addition of thrombin Whether this is referable to alteration in the fibrinogen or to changes in other plasma components¹⁰ is still unknown In either case such changes, spontaneously occurring or artificially induced, can conceivably affect the prothrombin time The decreased prothrombic activity of plasma stored for as much as four weeks is not necessarily due to changes in fibrinogen, however, since deprothrombinated, fibrinogen-free plasma can restore prothrombic activity to such plasma¹¹⁻¹³

TABLE 2 Hypoprothrombic Activity Related to Deficiency of Nonprothrombin Plasma Constituents in a Patient with Severe Obstructive Jaundice and Carcinoma of the Pancreas, with Extensive Metastases to the Liver

PLASMA MIXTURE*				PROTHROMBIN	
PARTS OF NORMAL PLASMA	PARTS OF PATIENT'S PLASMA	PARTS OF STORED NORMAL PLASMA†	TIME	ACTIVITY	
			sec	%	
fresh	barium sulfate	fresh	barium sulfate		
1	0	0	0	12 8	100 0±
0	1	0	0	>180 0	<1 0
0	0	1	0	22 6	10 0
0	9	1	0	33 8	50 0±
0	0	0	0	68 0	2 3
0	1	0	0	13 6	100 0±
0	0	0	1	21 8	12 0

*All plasmas oxalated

†Stored for twenty seven days at 4-5 C

‡Corrected for dilution with prothrombin free barium sulfate plasma

patient's plasma was far less able to rectify the prolonged prothrombin time of stored plasma than normal plasma was The plasma of Subject 2, with chronic myelogenous leukemia, behaved similarly (Table 3) Clearly, these subjects lacked a component (not prothrombin) present in fresh normal plasma that is necessary for normal prothrombic activity in the one-stage method and is deficient in stored plasma

*It is for this reason that the plasma must be fresh for the accurate determination of plasma prothrombin by the orthodox one stage procedure

It is probable that many similar observations will be made when more practical methods of measuring the labile factor, such as that of Stefanini and Quick,¹⁶ are widely applied. Prothrombic activity is distinctly decreased¹¹ when the concentration of this factor is less than 50 per cent of normal. Furthermore, the effect of suboptimal concentration of labile factor is more pronounced if the prothrombin is also below normal. Accordingly, an elevated prothrombin time of a given plasma sample may be due to deficiencies of prothrombin, labile factor or fibrinogen singly or in combination.

Other Plasma Components That Accelerate the Conversion of Prothrombin to Thrombin

To these variables must be added the accelerator globulin of Seegers,⁴ Factor V of Owren,³ prothrombin A of Quick² and plasma factor of Fantl and Nance.⁵ Apparently, these entities also accelerate the conversion of prothrombin to thrombin. Hemorrhagic episodes and hypoprothrombinemic activity due to deficiency of Factor V¹⁷ and prothrombin A² have been established. Furthermore, after acute liver poisoning by chloroform in dogs, not only prothrombin but also plasma accelerator globulin falls, contributing to the low plasma prothrombic activity.¹³ Here, too, the elevated prothrombin time, signifying a relatively retarded evolution of thrombin from prothrombin, reflected inadequacies in accelerator globulin as well as prothrombin.

Antithrombin In both the one-stage and two-stage techniques the thrombin evolved from prothrombin is assayed by its ability to convert fibrinogen to fibrin. Validity of this measurement depends upon the presupposition that no agent is present that will inactivate the evolved thrombin or otherwise interfere with its clotting of fibrinogen. This supposition is incorrect since plasma contains antithrombin, which can inactivate appreciable quantities of thrombin. The longer the thrombin is in contact with antithrombin, the greater the amount inactivated. Furthermore, heparin enhances this inactivation.¹⁹ Unfortunately, little is known regarding the plasma concentration of antithrombin or heparin, or both, under pathologic conditions. Conceivably, variations in plasma antithrombin or in circulating heparin or heparin-like anticoagulants, as in certain hemorrhagic disorders,²⁰⁻²¹ can influence prothrombic activity considerably. This would be especially true in hypoprothrombinemia in which the amount of thrombin evolved was so small or its evolution so slow that antithrombin activity could play a substantial role. To what extent plasma antithrombin activity may influence prothrombin time awaits further investigation.

Other clotting inhibitors Other circulating anticoagulants have recently been described²²⁻²³ that affect the rate of thrombin evolution from prothrombin. They may similarly affect prothrombin

determinations by the one-stage procedure. Considerable work is necessary to explore this possibility.

Serum prothrombic activity Some of the foregoing considerations bear particularly on the determination of serum prothrombin. Obviously, the absence of fibrinogen must be rectified. Furthermore, little is known concerning the concentration in serum of other important clotting constituents. We have found that under certain conditions labile factor may be considerably reduced, or may indeed disappear, during coagulation.²⁴

Coagulation is also attended by the appearance of substances that accelerate or activate the con-

TABLE 3 *Hypoprothrombic Activity Related to Deficiency of Nonprothrombin Plasma Constituents in a Patient with Chronic Myelogenous Leukemia*

PLASMA MIXTURE*				PROTHROMBIN	
PARTS OF NORMAL PLASMA		PARTS OF PATIENT'S PLASMA		TIME	ACTIVITY
fresh	barium sulfate	fresh	barium sulfate		
0	0	1	0	0	16.2
1	0	0	0	0	14.0
0	9	1	0	0	24.1
1	9	0	0	0	27.8
0	0	0	0	1	52.5
1	0	0	0	1	14.7
0	0	1	0	1	16.5
0	9	0	0	1	24.4
					27±
					100±
					97±
					78±
					3
					42±
					25±
					96±

*All plasmas oxalated.

†Stored for thirty-one days.

‡Corrected for dilution with prothrombin free barium sulfate plasma.

version of prothrombin to thrombin by thromboplastin and calcium.²⁵⁻²⁶ A mixture of plasma with serum devoid of prothrombin shows greater prothrombic activity than can be attributed to the plasma prothrombin in the mixture.²⁴⁻²⁶ The amount of the accelerator in serum is related to the amount of prothrombin consumed in the process of coagulation, and varies under pathologic conditions.²⁷⁻²⁸ Obviously, elaboration of this substance during clotting may affect appreciably the apparent prothrombic activity of serums. We have observed, for example, that after the coagulation of hemophilic blood, the serum often exhibits from 50 to 100 (or more) per cent of the original plasma prothrombic activity when measured by the one-stage procedure.²⁸ By the two-stage technic, however, far less serum prothrombin is demonstrable. Accordingly, determination of serum prothrombin concentration from serum prothrombin time may be erroneous. Furthermore, computations of the prothrombin consumed during coagulation from differences between plasma and serum prothrombic activities must be viewed with caution.

In view of the prothrombin-enhancing effect of serum every precaution should be taken in draw-

ing blood for prothrombin determination against partial coagulation, which may occur when venipuncture is not immediately successful and when the blood does not flow freely into the syringe

Weaknesses and Limitations Related to Thromboplastin Reagent

In determining prothrombin its conversion to thrombin by thromboplastin should not be limited by the quantity or quality of this clotting agent. Nevertheless, the source of thromboplastin and the method of its preparation profoundly affect the prothrombin time although it is presumably provided

This "normal control value" may not be representative of the average normal subject since marked variations in prothrombic activity may occur from person to person or in the same person from day to day. A given prothrombin time can be interpreted, therefore, only in the light of the range of values obtained with the same thromboplastin on a group of normal subjects.

It has also been reported that a given thromboplastin extract may show low potency when tested on whole plasma but good activity when tested on diluted plasma^{30, 31}. Similarly, under certain conditions diluted thromboplastin is more potent

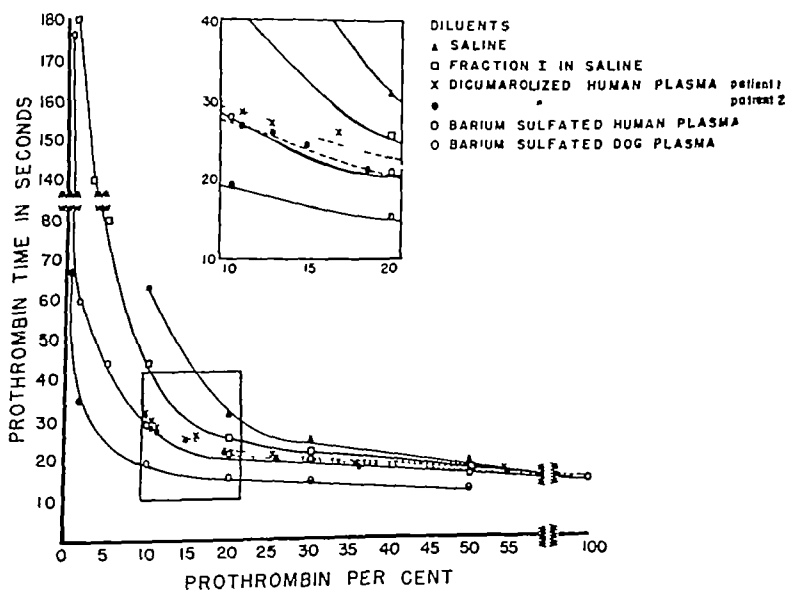


FIGURE 1 Relation between Prothrombin Time and Prothrombic Activity of Normal Human Plasma Diluted with Various Diluents

Fraction I in saline solution contained 500 mg of Harvard Fraction I per 100 cc. Patient 1 and 2 were subjects with myocardial infarction treated with dicumarol. Their plasmas, used as diluents, contained, respectively, 7.6 and 9.4 per cent (of normal) prothrombic activity. These figures were used in computing the prothrombin percentage in the dicumarolized plasma and normal plasma mixtures.

in excess. Quick²⁹ uses only fresh rabbit-brain extract, which for normal plasma gives a prothrombin time of 11.0 to 12.5 seconds. For practical reasons most clinical laboratories employ commercial thromboplastin preparations, which rarely give such a low prothrombin time and which vary considerably in potency from batch to batch even from the same manufacturer*. Furthermore, thromboplastin extracts deteriorate fairly rapidly in the liquid state. In view of these variations the prothrombin time of a given plasma sample has little significance unless it is accompanied by a value obtained with the same thromboplastin on a normal subject.

*This may be due to the presence of anticoagulants in thromboplastin extracts from brain.³²

than concentrated thromboplastin.³¹ Profound differences in prothrombin time are also obtained even on the same plasma when Russell-viper venom is used instead of brain extract.^{31, 32} From the foregoing, it is evident how considerable confusion regarding prothrombin concentration and prothrombic activity may arise owing to the use of different thromboplastin preparations.

Relation between Prothrombic Activity and Prothrombin Time

Fundamental to the one-stage method is the curve relating prothrombin time with prothrombic activity (Fig 1). From such curves the observed prothrombin time is translated into prothrombic ac-

tivity In the range of 25 to 100+ per cent (of normal) prothrombic activity a substantial reduction results in a very small increment in prothrombin time Therefore, conversion of a given prothrombin time into prothrombic activity is in this range only an approximation This has been strongly emphasized by Link.³³ Attempts have been made^{34, 35} to circumvent the difficulty by prior dilution of the test plasma to a range where a relatively small alteration in activity is reflected by a large change in prothrombin time In this way hypoprothrombinemia can be detected long before it becomes apparent from determinations on undiluted plasma

Dilution technic The diluent employed for this purpose is extremely important Ideally, it should be plasma that is devoid of prothrombin but normal in all other clotting components Dilution with saline solution, a procedure widely used,³⁵ is unsatisfactory because it dilutes other clotting factors as well as prothrombin Subnormal levels of these substances may thus become exaggerated, consequently affecting the prothrombic activity considerably The addition of fibrinogen to the diluent³⁶ assures adequacy of only one component When a saline solution of fibrinogen is used as diluent, the curve relating prothrombic activity with prothrombin time differs considerably from that derived with saline solution alone (Fig 1) Different curves are furthermore obtained when plasma is diluted with plasma that has been rendered prothrombin free by prior adsorption with barium sulfate (Fig 1) This agent removes prothrombin almost quantitatively as well as a small amount of nonprothrombin protein.²⁷ The question arises whether the additional material adsorbed consists of nonprothrombin clotting factors As far as we know, the smallest amount of barium sulfate required to adsorb the prothrombin does not remove other important plasma clotting constituents.*

Dicumarol decreases plasma prothrombin, presumably by inhibiting its production in the liver.³² Most investigators agree that other clotting factors are not affected to any considerable degree Plasma from a dicumarolized subject whose prothrombin has been markedly reduced should, therefore, be an ideal diluent in the determination of prothrombic activity of any unknown plasma The curves relating prothrombic activity with prothrombin concentration are practically identical when either dicumarolized or barium sulfate plasma is used as diluent (Fig 1) Furthermore, adsorbing dicumarolized plasma with barium sulfate does not alter the relation (Fig 2) This indicates that the adsorbing agent does not remove important clotting factors present in the dicumarolized plasma From the point of view of ready availability, barium sulfate

plasma is preferable to dicumarolized plasma as a diluting agent †

By the one-stage technic dog plasma shows greater prothrombic activity than human plasma.³⁹ By the two-stage procedure, however, the activities are essentially the same in both species.⁴⁰ Since there is no evidence that dog prothrombin differs in its reactivity from human prothrombin, the discrepancy is most likely referable, at least in part, to nonprothrombin factors In support of this interpretation is the fact that human plasma diluted with barium sulfate *prothrombin-free dog* plasma exhibits much greater prothrombic activity than that diluted with barium sulfate *prothrombin-free human* plasma (Fig 1) Similar results are obtained with

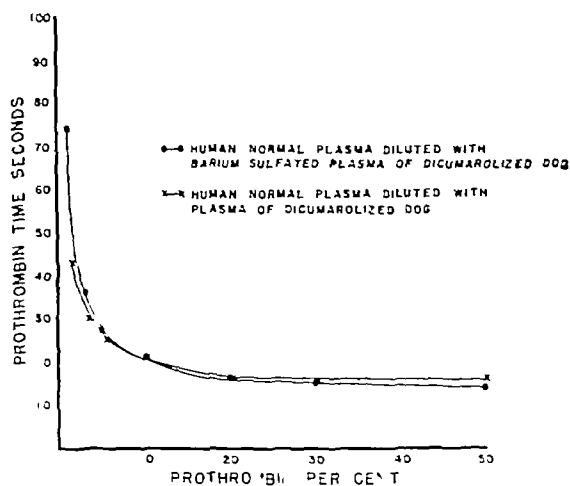


FIGURE 2 Comparative Effects of Dicumarol and Barium Sulfate on Plasma in Relation to Its Use as Diluent in the Determination of Prothrombin

The dog received a total of 18.7 mg of dicumarol per kilogram of body weight intramuscularly for twelve days before the experiment The prothrombic activity of the plasma, which was used as diluent, was 0.5 per cent

prothrombin-free rabbit plasma It is not clear whether this is due to the presence in these species of an as yet unknown factor not present in man or to larger amounts of known nonprothrombin clotting factors that influence prothrombic activity.‡ If the latter were true, barium sulfate dog or rabbit plasma might be preferable as a diluent in the one-stage procedure, since excesses of these factors might thus be assured

Some investigators have used plasmas rendered prothrombin free in other ways — namely, by ad-

*Barium sulfate is said to remove approximately 50 per cent of Factor V from plasma but how much is required to do this is not reported.³

†It should be mentioned that recent evidence suggests that dicumarol affects the clotting system of plasma in more ways than mere reduction in prothrombin.⁴¹ If this is so it is noteworthy that barium sulfate has the same effect.

‡Quick and Stefani⁴² have found that more labile factor is present in dog plasma than in human plasma.

sorption with aluminum hydroxide,^{6, 41} with tricalcium phosphate¹⁷ or by passage through Seitz filters.³ Before these procedures can be evaluated one should know whether or not they also affect the nonprothrombin-clotting components.

The preparation of barium sulfate plasma requires complete separation of the adsorbing agent since residual traces may affect, by continued adsorption, the prothrombin of the test plasma that is diluted.⁴² This probably holds true also when other adsorbing agents are used.

It should be remembered, furthermore, that the labile factor is at least just as labile in prothrombin-free as in whole plasma. Accordingly, the deprothrombinated plasma should be used shortly after preparation. We have found barium sulfate plasma fully potent for at least five hours if it is kept refrigerated.

Other Important Variations in the One-Stage Procedure

The prothrombin time is considerably influenced by the order with which the reagents are mixed. In most laboratories thromboplastin and calcium are added to plasma. In others, however, the order is reversed.⁴³

It should be pointed out also that 0.02M calcium chloride, the concentration generally used in the prothrombin determination, has recently been found inadequate for dicumarolized plasma²⁹; 0.025M calcium chloride is recommended instead. In the light of this finding older studies of the effects of dicumarol will need re-evaluation.

TWO-STAGE METHOD

General Procedure

The two-stage technic is based upon *complete* conversion of prothrombin to thrombin by thromboplastin plus calcium. The yield of thrombin is subsequently measured. By definition, 1 unit of prothrombin gives 1 unit of thrombin, and 1 unit of thrombin is that amount which will clot 1 cc of a standard fibrinogen solution in fifteen seconds at 28°C.⁸

In the determination the test plasma is defibrinated by the addition of a small amount of thrombin, excesses of which are inactivated by incubation. The mixture is then diluted serially with saline solution, the dilutions are treated with thromboplastin and calcium, and the resultant mixtures allowed to stand until conversion of prothrombin to thrombin is complete. They are then reacted with a solution of fibrinogen. A sample of the dilution that induces coagulation in fifteen seconds is considered to contain 1 unit of thrombin. From the dilution the concentration of thrombin (in units), or its precursor, prothrombin, is computed.

Weaknesses and Limitations

Antithrombin Perhaps the most serious limitation of the two-stage procedure is in the determination of plasma prothrombin when its concentration is low. With relatively normal prothrombin levels the method calls for high dilution of the plasma. Hypoprothrombinemic plasma, however, must be diluted *less* than normal plasma to furnish a mixture that will yield sufficient thrombin to clot the standard fibrinogen solution in the required time. Because of this, thrombin inactivation by antithrombin may become formidable, leading to gross inaccuracies. The lower the prothrombin, the greater the question of antithrombin activity looms. For clinical purposes, where interest is focused largely on hypoprothrombin conditions, this drawback makes the procedure of limited value. A method to circumvent antithrombin activity has been reported,⁴⁴ but experience with it has been limited.

Importance of nonprothrombin factors affecting the evolution of thrombin In the two-stage procedure *complete* conversion of prothrombin and measurement of the evolved thrombin is assumed *before* the influence of antithrombin supervenes. As mentioned above, Ware and Seegers⁴ have shown that prothrombin conversion is both retarded and incomplete when accelerator globulin is decreased or absent. This may occur under certain pathologic conditions in which hypoprothrombinemia has also been observed.¹⁸ The serious effect of antithrombin when thrombin evolution is slow has already been discussed. Seegers et al.^{18, 45} have accordingly modified the two-stage method by providing supplements of accelerator globulin.

Other factors have recently been described (Factor V of Owren⁸ and labile factor²), which similarly accelerate the conversion of prothrombin to thrombin. The question arises whether they too should be provided to a test plasma to assure complete as well as rapid prothrombin conversion. Since none of them are available commercially, they would have to be prepared independently—a laborious task. Otherwise, deprothrombinated plasma must be added to the prothrombin-thromboplastin-calcium reaction mixture, a procedure not unlike the dilution technic of the one-stage method. This would introduce the untoward effects of antithrombin.

Serum prothrombin These considerations bear significantly on the two-stage determination of serum prothrombin. As pointed out above, serum not only is devoid of fibrinogen but also frequently contains suboptimal amounts of labile factor.⁴⁴ Furthermore, accelerator globulin is relatively unstable in human serum.⁴⁵

Also to be considered is evidence indicating that thrombin is capable of destroying prothrombin.⁴⁶ It will be recalled that in the two-stage procedure the test plasma is first defibrinated by additions of

thrombin In serum, also, thrombin has been evolved as a consequence of coagulation To what extent this clotting agent, added or spontaneously elaborated, affects the prothrombin in question requires further elucidation

Laboriousness of the two-stage technic Practically all investigators agree that the two-stage technic is much more laborious than the one-stage procedure This precludes its routine use in most clinical laboratories

AIMS AND ORIENTATION OF THE PHYSICIAN

The physician who requests a prothrombin determination should have a clear idea of the information he seeks Does he want to know the precise concentration of this factor in contradistinction to other clotting constituents? Or does he seek an over-all appraisal of the ability of the plasma to evolve thrombin, which may help him detect a more general coagulation defect underlying a hemorrhagic disorder? And, above all, the physician prescribing dicumarol for the prevention or treatment of thromboembolic disease wants to know the effective, yet safe, "prothrombin level," whether his patient is within that range, and how he can be kept there consistently It should be emphasized that one who undertakes anticoagulant therapy tampers with one of the most important homeostatic functions of the body, and that dicumarol strikes at the keystone in the mosaic of the blood clotting mechanism

And how should the physician interpret the results reported by the laboratory? Considerable confusion exists in the minds of practitioners regarding the terms "prothrombin per cent," "prothrombin time," "normal control," "diluted prothrombin time," "prothrombin activity" and "clotting time" and their relations to each other

Confusion would be avoided if a sound and simple modification of the two-stage procedure were available since with this technic quantitation is in terms of clearly defined units For various reasons, some of them discussed above, this procedure is employed in very few clinical laboratories

At the risk of repetition the above terms are reconsidered "Prothrombin time" is an empiric interval representing the minimal time required for oxalated or citrated plasma to clot when provided with optimal amounts of thromboplastin and calcium Practically speaking, it bears no relation to the clotting time of whole blood, or to the clotting time of recalcified plasma (recalcification time) In normal subjects it may be between 12 and 14 or more seconds, depending upon individual variation in prothrombic activity and upon the thromboplastin preparation used in the determination

"Prothrombin concentration" refers to the actual level of prothrombin in the plasma, and is expressed in percentage ("prothrombin per cent") of what is

found in normal subjects* This must be distinguished from "prothrombin activity," or, as we propose, "prothrombic activity," which indicates the over-all ability of plasma to form thrombin in the presence of optimal thromboplastin and calcium, reflecting the activities not only of prothrombin but also of nonprothrombin clotting factors

Prothrombic activity, also expressed in percentage of normal, is calculated by interpolation of the observed prothrombin time on a standardization curve, that relates prothrombin time with various degrees of dilution of normal plasma Different curves are obtained with different diluents The advantage as diluent of prothrombin free, yet otherwise normal, plasma is that it assures normal amounts of nonprothrombin clotting factors, thus permitting determination of actual prothrombin concentration The prothrombin concentration of a test plasma can be computed from the prothrombin time observed on the plasma similarly diluted with the prothrombin free plasma As far as we can determine, barium sulfate plasma approaches the ideal diluent most closely

Lowering the concentration of prothrombin or various plasma clotting components results in little increase in the prothrombin time until prothrombic activity is about 25 per cent of that found in the average normal subject The difference in prothrombin time between plasma containing 50 per cent of normal prothrombic activity and 100+ per cent is practically within the limits of accuracy of the measurement Accordingly, reports of prothrombic activity (as determined on *whole* plasma) in this range have little significance except to indicate that the activity is above 50 per cent

Determinations on diluted plasma ("diluted prothrombin time") are more precise and are especially useful in the range of prothrombic activity exceeding 15 per cent of normal Below this, little is gained by this modification, since sufficient accuracy is obtained by determining the prothrombic activity on whole plasma If, however, information is desired concerning the concentration of prothrombin itself rather than of its activity in conjunction with nonprothrombin factors that also affect the prothrombin time, dilution with prothrombin free (yet otherwise normal) plasma offers distinct advantages

It is important to recognize the wide variation in the prothrombic activity of normal persons The "control value," obtained on one normal subject and reported side by side with the value given for a test plasma, serves merely to indicate the potency of the thromboplastin reagent used, and by no means as a basis for strict comparison

Experience indicates that when prothrombic activity exceeds 20 per cent of normal, hemorrhage is rarely, if ever, due to deficiency of prothrombin, its activators or fibrinogen This degree of hypo-

*In the two-stage technic prothrombin concentration is expressed in units. Normal human plasma is said to contain 300 units per cubic centimeter

prothrombic activity can be readily detected by measurements on undiluted plasma

Frequently it may be desirable to determine whether the clotting defect is due to low prothrombin per se or to inadequacy of the other factors belonging to the prothrombin constellation*. This can be done by simultaneous determinations with the nonprothrombin factors provided (by diluting with prothrombin-free normal plasma) and without providing these factors (by determining prothrombin on the undiluted plasma). If low activity is due to deficiency of prothrombin alone the results will agree

It has been repeatedly observed that the prothrombin time of dicumarolized subjects fluctuates sharply. Many of the reasons for this are clear. In a dog that receives a large dose of the drug about 80 per cent of the plasma prothrombin disappears within twenty-four hours (Fig 3). The remaining 20 per cent is still sufficient to give a relatively normal prothrombin time since the difference in prothrombin time between plasma with 100 per cent prothrombin and that with 20 per cent is only slight (Fig 1). During the next ten hours the prothrombin continues to decline precipitously and reaches suffi-

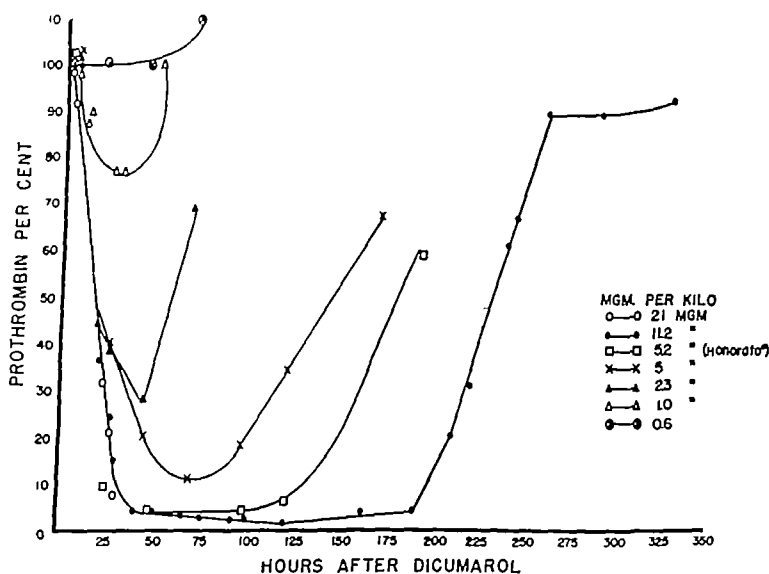


FIGURE 3 Effect of Varying Doses of Dicumarol on the Plasma Prothrombin Concentration in the Dog

All observations, with the exception of those of Honorato,¹² were obtained on the same animal. Dicumarol was administered intramuscularly as a suspension in propylene glycol.

closely. If, however, the low activity is referable to nonprothrombin factors, the value obtained by the dilution technic will be higher (after correction for dilution) than that obtained on undiluted plasma.

The estimation of prothrombic activity in the patient who is about to receive, or is receiving, dicumarol deserves special consideration. The drug apparently acts by blocking prothrombin synthesis in the liver. The goal of therapy is reduction of circulating prothrombin to a level where intravascular clotting is prevented or stopped, but not to the point where hemorrhage is likely to ensue. Obviously, a delicate balance must be attained between the velocity with which prothrombin disappears from the blood after its formation is blocked and the speed with which it is regenerated when the drug is eliminated.

ciently low levels to give markedly elevated prothrombin times.

If dicumarol had been given to an animal with a prothrombic activity of only 30 per cent or less (of normal), the drug would have induced an elevated prothrombin time within a much shorter interval. Since determinations by the orthodox technic could hardly have distinguished with certainty between 30 per cent prothrombin and 100 per cent the quicker effect might have been attributed to undue sensitivity to the drug. This indicates the importance of knowing prothrombic activity precisely before dicumarol administration.

The regeneration of prothrombin when the effects of dicumarol are wearing off is equally rapid (Fig 3). An elevated prothrombin time can return very quickly to a relatively normal one without necessarily indicating restoration of 100 per cent of the

*For the purposes of this paper fibrinogen is included in this constellation.

prothrombic activity. If to these considerations are added differences in the weights of patients,* possible variations in rate of absorption† of the drug from the intestinal tract, and individual variations in liver function or other bodily functions controlling prothrombin synthesis and dicumarol elimination,‡ one can readily understand the wide and sharp fluctuations in plasma prothrombic activity often observed during dicumarol therapy.

The conclusion appears inescapable that the best guide to dicumarol therapy is frequent and precise determinations of prothrombic activity as well as prothrombin concentration. In the range of 15 to 100+ per cent of prothrombin (12-second to 16-second prothrombin time) precision can best be attained by the use of a proper dilution technic.

It is difficult to state what concentration of prothrombin is both "safe" and effective in prevention or treatment of thromboembolism. The literature is replete with recommendations that a prothrombin time of between 30 and 40 seconds, or that a level of 20 per cent of prothrombin, should be maintained. While experience indicates that a prothrombin time of 30 to 40 seconds is safe in persons with otherwise normal hemostatic function, it may be hazardous in the presence of other disturbances in the hemostatic mechanism. Furthermore, such a prothrombin time has little significance unless the potency of the thromboplastin used is known from prior standardization on normal subjects. Also, many of the reports recommending a prothrombin concentration of 20 per cent are based upon saline dilution curves. In the light of the advances made in the determination of prothrombin this figure is no longer tenable.

In our experience a prothrombin concentration of between 5 and 10 per cent of normal (obtained by the procedure outlined below) can usually be regarded as safe. Also, at this level coagulation is defective.²⁴ How effective this is against thrombotic disorders requires further clinical observation.

RECOMMENDED PROCEDURE FOR PROTHROMBIN DETERMINATION

The method that we consider at the present time most satisfactory for general clinical use in the determination of prothrombin is outlined in detail. The technic is essentially the one-stage method of Quick as modified by Rosenfield and Tuft.²⁵

Thromboplastin extract (prepared from Difco thromboplastin⁴⁶) is pipetted in 0.1-cc amounts into each of many prothrombin-time test tubes, which are then stored at -10°C until used. The extract thus stored in the frozen state in ready-to-use units retains its potency for as long as seven months.⁴⁶ To standardize it, prothrombin times on a plasma

pool from at least 5 normal subjects are determined with each batch according to the following technic.

Barium sulfate plasma§ To each cubic centimeter of fresh normal plasma is added 0.1 gm of powdered barium sulfate (C.P.). The mixture is shaken, placed in the incubator at 37°C for fifteen minutes, during which it is shaken frequently, and then centrifuged for thirty minutes at 3000 r.p.m., after which the supernatant is carefully separated. This barium sulfate plasma, used as the diluent, should be kept at refrigerator temperature ($+5^{\circ}\text{C}$) and should be used within five hours of preparation.

Standardization curve Various dilutions are made of the pooled normal plasma with the barium sulfate plasma, 0.10 cc of each of the dilutions is added to a thromboplastin tube that has been thawed for ten minutes in the water bath at 37°C , 0.10 cc of 0.025M calcium chloride is squirted in from a tuberculin syringe, and the time of clotting observed while the mixture is constantly agitated with a wire loop. The standardization curve relating the prothrombin time with the prothrombin concentration in percentage is obtained by plotting the observed prothrombin times against the percentage of normal plasma in the normal plasma-barium-sulfate plasma mixtures.

Determination of prothrombin concentration of the test plasma Of the test plasma 0.10 cc is mixed with 0.90 cc of fresh (no more than five hours old) normal plasma treated with barium sulfate as described above, 0.1 cc of the mixture is added to a thromboplastin tube, and calcium chloride solution added as described above. From the observed prothrombin time of the mixture, the percentage prothrombin is interpolated from the standardization curve. This value, multiplied by 10 to correct for the 1:10 dilution, gives the prothrombin concentration of the undiluted plasma in percentage of normal.

For extremely hypoprothrombinemic plasma a smaller dilution may be necessary (0.4 cc of test plasma to 0.6 cc of barium sulfate plasma). Under such conditions the appropriate dilution correction must be made.

Determination of prothrombic activity In the determination of prothrombic activity on undiluted plasma, the procedure is the same, omitting dilution with barium sulfate plasma. The results are similarly interpolated from the standardization curve described above, and are expressed as prothrombic activity in percentage of normal.

Determination of serum prothrombic activity To 0.7 cc of barium sulfate normal plasma 0.3 cc of oxalated serum, incubated at 37°C for half an

*Note in Figure 3 the differences in degree and duration of dicumarol action in relation to size of dose per kilogram of body weight.

†In man dicumarol is given exclusively by the oral route.

‡Little is known regarding prothrombin synthesis or dicumarol elimination both of which can conceivably be greatly influenced by the underlying disease or its complications.

§All plasmas are from blood oxalated with 1 cc. of 0.1M sodium oxalate to 9 cc. of blood.

hour to inactivate thrombin, is added. The prothrombin time is determined on 0.1 cc of the mixture in the usual manner, the result interpolated from the standard curve, and the dilution correction applied.

SUMMARY

The available methods for determination of plasma prothrombin are scrutinized in the light of recent advances in knowledge of prothrombin, its activators and accelerators, and its role in the coagulation of blood. Since several nonprothrombin components as well as prothrombin have a profound effect on the velocity of thrombin evolution from prothrombin or on the amount formed and available for clotting fibrinogen, great caution must be exercised in drawing conclusions regarding actual prothrombin concentrations from one-stage prothrombin times or from two-stage prothrombin determinations.

Other weaknesses and limitations of prothrombin methods are discussed, the aims and orientation of the physician are considered, and the most satisfactory clinical laboratory method for prothrombin determination is described.

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PARTIAL URETERAL OBSTRUCTION*

Its Effect on Urinary Excretion

GEORGE J WARREN, M D,† AND JOSEPH M LOONEY, M D‡

WEST ROXBURY, MASSACHUSETTS

A PATIENT with a unilateral ureteral stricture afforded an unusual opportunity to observe the effects of partial obstruction on urinary excretion and the changes in excretion subsequent to its relief. The stricture followed a ureterolithotomy done in the presence of marked infection of the ureter and kidney above the level of the obstructing calculus. A brief report of this case follows.

W S D., a 49-year-old white salesman, was admitted to the West Roxbury Veterans Hospital in October, 1947, for the third time with symptoms of frequency, nocturia and a persistent dull ache in the right flank.

This illness had begun 2½ years previously, when he had been studied at this hospital for total hematuria of 3 days' duration. The hematuria had subsided at the time of entry to the hospital. An x-ray film of the abdomen had revealed

The third admission occurred approximately 6 months after the ureterolithotomy with drainage. In the interim he had been fairly well but had recently noted a loss of energy, some burning on urination, frequency and nocturia. There had been no episodes of fever or acute pain in the right flank.

Physical examination showed that the patient was not in acute distress. There was a well healed, right subcostal scar. There was no costovertebral-angle tenderness. The voided urine was cloudy and contained numerous pus cells. There was no residual bladder urine. Retrograde ureteral catheterization revealed an impassable obstruction in the right ureter at the level of the previous surgical incision. There was considerable hydronephrosis and hydroureter above.

The temperature and pulse were normal, and the blood pressure was 145/95.

Studies of the blood showed a calcium of 10.2 mg, phosphorus of 2.8 mg, uric acid of 3.9 mg and total protein of 7.33 gm per 100 cc. The alkaline phosphatase was 2.0 Bodansky units. A culture of the bladder urine showed the presence of *Aerobacter aerogenes*.

TABLE 1 Preoperative Study

KIDNEY	URIC ACID	PHOSPHORUS	CALCIUM	pH	PHENOLSULFONEPHTHALEIN		CULTURE
	mg /100 cc.	mg /100 cc	mg /100 cc		APPEARANCE TIME min	QUANTITATIVE TEST mg /cc	
Right	12.0	16.1	21.9	7.5	0	0	<i>A. aerogenes</i> Sterile
Left	26.0	69.0	20.5	6.9	3	0.05	

several opacities in the region of the right kidney, but the patient had refused further investigation and had been discharged without a complete study.

In March, 1947, he was admitted to the hospital for the second time. There had been no major urinary symptoms during the 2 years between the first and second admissions. At this second admission he complained of severe pain in the right flank of several days' duration. He was acutely ill and had marked tenderness in the right costovertebral angle. Studies revealed a semiopaque calculus in the upper right ureter. At operation a stone located approximately 8 cm below the ureteropelvic junction was removed. Because of marked infection of the ureter, T-tube drainage of the ureter and kidney was instituted. The tube was removed 2 weeks later, after several days of urinary leakage, the wound became dry and healed, and the patient was discharged in June, 1947. On analysis the calculus was found to be of the mixed type.

On November 14 the right upper ureter was explored. The ureter was imbedded in extensive scar tissue, and approximately 8 cm below the ureteropelvic junction there was a dense stricture, which did not admit the tip of a small duct probe. The ureter above was moderately dilated. A small segment of ureter containing the stricture was excised, and an end-to-end anastomosis performed over the upper arm of a T-tube, which was brought out at the lower angle of the incision. The tube was removed 6 weeks after operation. The fistulous tract healed rapidly, without urinary leakage, and the patient was discharged in December, free of symptoms.

Before the second operation studies were made of the urinary excretion from each kidney. An open-ended No. 6 Fr catheter was passed up each ureter. These were used so as to tamponade the ureteral walls and thereby direct the entire volume of urine through the collecting catheters. The left catheter was passed to the renal pelvis. There was obstruction to the passage of the right catheter at the level of the stricture, and the tip of the instrument appeared to have fixed itself within the stricture site. The flow from both catheters was free and abundant. Specimens were collected in test tubes of equal size. By observation of the levels of urine in each test tube at regular intervals, it was noted that

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†Senior resident surgeon, Veterans Administration Hospital.
‡Director of clinical laboratory, Veterans Administration Hospital.

approximately equal quantities of urine were being excreted by each kidney. By such a rough estimation it was assumed that the volume excretion per minute of the affected right kidney closely paralleled that of its normal mate. The amounts of uric acid, calcium, phosphorus and phenolsulfonephthalein were determined. There was a distinct difference in the quantities of these substances excreted in the urine from the right and left kidneys. The results of the analysis of each specimen are given in Table 1. Values are recorded in milligrams per 100 cc. The quantitative phenolsulfonephthalein is given in milligrams per cubic centimeter

The same studies were made on a control subject with a normal upper urinary tract. The patient was a young man who had been admitted to the hospital for investigation of long-standing enuresis. Individual urine specimens were obtained from him during the course of the examination. Blood chemical values were within normal limits throughout. The several values recorded for each kidney of a normal control subject closely paralleled one another. The figures for each kidney are given in Table 3.

DISCUSSION

Final conclusions cannot be drawn from observations on a single case. However, the findings in this case suggest several points of interest when compared with the results of studies made by others. The excretion of normal urine is directly dependent upon the functional integrity of the tubular system. Hayman¹ and Gamble² state that the excretion of phenolsulfonephthalein and diodrast appears to be primarily a function of the tubules. Of the amounts



FIGURE 1 *Intravenous Urogram Taken before Ureteroplasty*

It is interesting to note that the chemical values recorded for the affected right kidney were strikingly lower than those for the normal left kidney, even though the volume of urine excreted was the same. The only exception was the quantity for calcium, which was even a fraction higher than that on the left.

Six months after the plastic repair of the right ureter these studies were repeated. In addition an intravenous urogram taken before operation (Fig. 1) was compared with a direct pyelogram taken 5 weeks after operation (Fig. 2). Films taken 6 months after ureteroplasty demonstrated more rapid excretion and a better concentration of the dye in the right kidney (Fig. 3).

Postoperatively, both urine specimens were collected from the renal pelvis, since there was no further obstruction to the passage of the No. 6 Fr. catheter up the right ureter. The values obtained showed a more normal relation between the urine excreted from the right and that from the left kidney (Table 2).

It will be noted from Table 2 that the postoperative values recorded for the affected right kidney more closely approximated those for the normal left. Particularly striking were the figures for phenolsulfonephthalein appearance time and quantitative phenolsulfonephthalein. Previously, these values had been zero on the right.



FIGURE 2 *Direct Pyelogram Taken Five Weeks after Operation*

given for functional tests approximately 90 per cent of both phenolsulfonephthalein and diodrast is excreted by the tubular system, and only 10 per cent passes through as glomerular filtrate. When given in test doses the bulk of phenolsulfonephthalein and diodrast is bound by adsorption to the plasma proteins. Because of this link, tubular activity is required to effect a separation and excretion of these plasma-bound substances. In the case presented

above, the fact that preoperatively no phenolsulfonephthalein and very little diodrast were excreted by the affected kidney suggests a greatly altered tubular physiology. The probable cause for this altered function was an increased intrapelvic pressure secondary to partial ureteral obstruction. That this sequence of events—obstruction, back pressure and tubular dysfunction—had occurred is further supported by the successful attempt at restoration of normal tubular function during the six months following operation for relief of the obstruction. This is brought out by comparison of the respective values given in Table 1 and 2. Hinman,³ in his studies on hydronephrosis, has clearly demonstrated the structural changes in the tubules that follow hydronephrosis secondary to complete or partial urinary obstruction. The concomitant and subsequent functional change was shown to be one of gradual dilution and diminution of total volume of urine excreted.

Another observation worthy of note is the variation in the calcium level in the preoperative and postoperative study. Urinary stasis, secondary to obstruction of whatever type, has long been recognized and accepted as a definite predisposing factor in the formation and in the recurrence of renal calculi. Higgins,⁴ in discussing factors in the recurrence of renal calculi, noted that many recurrences followed a previous ureterolithotomy. Of these, a significant percentage of cases showed a secondary stricture at the operative site. Rolnick and Singer,⁵ working with dogs in a study of the effects of overdistention of the renal pelvis and ureter, demonstrated the structural damage that can occur to both medulla and cortex with various degrees of increased intrapelvic pressure. They noted also that in the urine from a blocked kidney there was a distinct diminution of the chloride content and an increase in the urea content as compared with the unobstructed side. Since the majority of calculi contain calcium to a greater or lesser degree, the urinary

ciated with an increased urinary calcium, a lowered calcium output was noted in kidneys with marked pathologic changes. This observation suggests that stone-forming tendencies are greater early in the



FIGURE 3 Urogram Taken Six Months after Operation

course of disease of the tubular system than in the irreversible or decompensated stage. Hunner,⁷ in 1924, noted the frequency of ureteral calculi in cases with proved ureteral stricture. In a later

TABLE 2 Postoperative Study

KIDNEY	URIC ACID	PHOSPHORUS	CALCIUM	pH	PHENOLSULFONEPHTHALEIN APPEARANCE TIME	QUANTITATIVE TEST	CULTURE
	mg /100 cc	mg /100 cc	mg /100 cc		min.	mg /cc	
Right	7.5	20.8	8.82	6.8	436	0.0214	<i>A. aerogenes</i>
Left	6.5	56.7	9.31	5.6	312	0.0425	<i>A. aerogenes</i>

excretion of this element is of particular interest. A stone-forming kidney probably excretes a greater amount of calcium salts than a normal one. Flocks,⁶ in 1939, reported analyses of individual urine specimens taken from "stone-bearing" kidneys and their normal mates. Values for urinary calcium were found to be greater in the stone-forming kidneys. Furthermore, the study revealed that a slight pathologic change in the kidney was usually asso-

paper he⁸ emphasized the role of urinary stasis as a major etiologic factor in calculi in the upper urinary tract.

In the majority of studies, attention has been directed to local conditions as possible causes of renal stones, but consideration must be given to systemic conditions as well. The frequent occurrence of uric acid, and occasionally cystine stones, indicates something other than local factors in such patients. Al-

bright et al,⁹ in an extensive study on hyperparathyroidism, clearly showed the direct relation of this systemic disease to frequent and recurrent formation of renal calculi in patients with surgically proved parathyroid tumors or hyperplasia. The systemic disturbance in the metabolism of calcium and phosphorus results in an increased excretion of these elements in the urine. A calculous nidus in the kidney, being constantly bathed in a highly concentrated solution of these substances, will have ideal conditions for the gradual formation of a calculus. Such patients usually exhibit bilateral stones either concurrently or alternately.

In most patients the formation of unilateral recurrent calculi cannot be explained on the basis of

of the right kidney in the case presented, preoperatively, the probability of a nephrectomy was considered. The finding of a short, partially obstructing stricture at operation prompted the course of treatment employed. That this procedure was justified is evidenced by the structural and functional improvement of the affected kidney in the six months following operation.

SUMMARY

A study on partial ureteral obstruction and its effect on urinary excretion is presented. Quantitative analyses of uric acid, phosphorus, calcium and phenolsulfonephthalein in the urine specimens from a partially obstructed kidney and its normal mate

TABLE 3 Control Study

KIDNEY	URIC ACID	PHOSPHORUS	CALCIUM	PH	PHENOLSULFONEPHTHALEIN		CULTURE
	mg/100 cc	mg/100 cc	mg/100 cc		APPEARANCE TIME min	QUANTITATIVE TEST mg/cc	
Right	45.6	18	28.9	4.5	5	0.49	Sterile
Left	46.2	16.5	29.7	4.5	5	0.50	Sterile

systemic disease alone. In these patients, who show no evidence of systemic disease, local factors appear to be responsible for the calculi. The exact mechanism of the process is obscure. Of the many recognized entities, urinary stasis and back pressure seem to be highly significant ones. In a decompensating or decompensated kidney, resulting from back pressure, the tubular physiology is greatly altered. In the case reported above, there was definite evidence of disturbed tubular function as shown by the failure of the affected kidney to excrete phenolsulfonephthalein and diodrast preoperatively. Furthermore, the wide variation in the amounts of other substances excreted is further evidence of tubular dysfunction. Despite this apparent failure of the tubular system the amount of calcium excreted was slightly higher than that of its normal mate. These findings suggest the possible relation of abnormal tubular physiology to the formation of renal stones.

Another point brought out by this case study is that regarding the value of reconstructive surgery to conserve renal tissue. Dodson¹⁰ has reported a large series of cases in which corrective surgery has resulted in the reconstruction of relatively good structural and functional kidneys. Because of the structural distortion and marked loss of function

were made. It was found that there was a marked diminution in the excretion of all these elements except calcium in the urine from the affected kidney. This wide variation disappeared after relief of the obstruction. Inferences regarding altered tubular function and increased tendency to stone formation are drawn from the data presented. Early recognition and treatment of obstructing lesions of the urinary tract may obviate the subsequent occurrence of a more serious disease.

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MUMPS COMPLICATED BY MYOCARDITIS, MENINGOENCEPHALITIS AND PANCREATITIS

Review of the Literature and Report of a Case

JOHN H. BLAND, M.D.*

BURLINGTON, VERMONT

MUMPS is usually considered to be an acute systemic disease of specific viral etiology with a special predilection for the parotid glands. The common complications are orchitis, pancreatitis, oöphoritis, mastitis and meningitis or meningoencephalitis, or both. Myocarditis has until the past few years been considered a rare and unusual complication. Several studies recently made call attention to the occurrence of myocarditis during the convalescent course of epidemic parotitis.

It is the purpose of this paper to submit a case report as additional evidence to support the belief that mumps is a generalized infectious process and that the myocardium and pericardium may be involved by an acute, infectious process of viral etiology, such affections may occur with varying frequency and may be of any varying severity. A discussion of the importance and implications of the studies made in the past few years is offered.

Pujol¹ first suggested in 1918 that myocarditis might be a complication of mumps. He reported 3 cases, each of which manifested clinical evidence of myocardial involvement, however, he lacked electrocardiographic confirmation. In 1925 Barbato² suspected mumps myocarditis on the basis of clinical observation. Manca,³ in 1932, was the first to report pathological sections in a case of acute, interstitial, fibrinous myocarditis occurring in a fatal case of mumps. He believed that this was a typical tissue reaction to the mumps virus. Wesselhoeft⁴ reviewed progress in mumps in 1942 and at that time noted the evidence of its being a systemic disease with a predilection for certain tissues. He remarked on the frequency with which clinical and subclinical mumps meningoencephalitis was unrecognized. The complement-fixation test for mumps virus on cerebrospinal fluid or blood serum and the dermatologic sensitivity test of Enders and his co-workers⁵ were discussed. Wendkos and Noll,⁶ in 1944, reported a case of mumps myocarditis diagnosed only by a chance electrocardiogram. They noted minor T-wave changes, bradycardia and lengthened PR interval, which was clearly temporarily shortened by atropine as is first-degree heart block secondary to active rheumatic carditis. Rosenberg⁷ reported an epidemic study in which electrocardiographic evidence of cardiac involvement was noted in 16 of 104 cases of mumps, or

15.4 per cent. Changes in the tracings (done serially) all occurred between the fifth and tenth days of illness, and returned to normal in from two to thirty-five days. Only 4 of the 16 patients had clinical evidence of cardiac involvement. Seven of the 16 had acute orchitis as a complication. This author points out how the implications reached pertain to rheumatic fever. He suggests that in the majority of cases mumps myocarditis follows a subclinical course and requires electrocardiographic studies for its recognition. He noted changes of varying magnitude in all complexes, but no specific pattern was noted. Fellnor and Pullen⁸ added another case with clinical and electrocardiographic evidence of myocarditis. There are many reports, such as that of Holden, Eagles and Stevens,¹⁰ describing central-nervous-system involvement in mumps. Bruenn¹¹ has reported on the mechanism of impaired auriculoventricular conduction in acute rheumatic fever, and Keith¹² studied overstimulation of the vagus nerve in rheumatic fever, emphasizing the nonspecific nature of PR-interval prolongation. Saphir¹³ reported myocarditis in bronchiectasis and noted the discrepancy between pulse rate and a slight elevation of temperature. The PR interval has been reported prolonged in other acute infectious diseases such as pneumonia, scarlet fever, diphtheria and measles.

The following case is reported as an instance of a complication of mumps and as additional evidence that the infection is a generalized disease.

CASE REPORT

J. H., a 55-year-old man, was admitted to the hospital on June 2, 1947, with a history of epigastric discomfort and a sense of expanding pressure, high in the epigastrium, of 2 days duration. This was exaggerated by effort, but was described as "indigestion." In about 2 hours marked nausea, vomiting and extreme weakness, which lasted 48 hours, followed. The patient vomited or retched every 15 or 20 minutes during this time. On the first night of the illness he was unable to lie flat in bed because of a choking sensation and dyspnea, relieved by sitting up on the edge of the bed. He complained of marked apprehension. Two episodes of syncope of 1 or 2 minutes' duration occurred on the day of admission. (This had never happened before.) He had chilly sensations and reported that he had a temperature of 102°F. He came to the hospital because of the dyspnea, which interfered with his work as a refrigerator repairman. On the day of admission, he developed a severe pulsating headache, located in the vertex, which continued for 5 days and finally subsided spontaneously. The patient was very lethargic and mildly disoriented. Marked anorexia was present for many days.

A careful review of the systems was not helpful. The past medical history disclosed nothing significant, and the family

*Fellow in cardiovascular research, University of Vermont College of Medicine.

bright et al,⁹ in an extensive study on hyperparathyroidism, clearly showed the direct relation of this systemic disease to frequent and recurrent formation of renal calculi in patients with surgically proved parathyroid tumors or hyperplasia. The systemic disturbance in the metabolism of calcium and phosphorus results in an increased excretion of these elements in the urine. A calculous nidus in the kidney, being constantly bathed in a highly concentrated solution of these substances, will have ideal conditions for the gradual formation of a calculus. Such patients usually exhibit bilateral stones either concurrently or alternately.

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The literature on this subject is reviewed, and electrocardiographic study, when possible, is recommended in all infectious diseases

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LEFT VOCAL-CORD PARALYSIS ASSOCIATED WITH HYPERTENSIVE HEART DISEASE

WILLIAM C L DIEFENBACH, M D *

ALBANY, NEW YORK

LEFt vocal-cord paralysis is frequently observed in various forms of intrathoracic disease, such as aortic aneurysm, mediastinal tumors, pleuritic thickening and pulmonary tuberculosis. A variety of cardiac lesions, including mitral stenosis, arteriosclerotic heart disease, congenital heart disease and aneurysms of the large vessels, may also produce this syndrome. Its occurrence in only a small percentage of cardiac conditions is not clear.

Although a number of hypotheses have been proposed, the exact mechanism has not been elucidated. Ortnier,¹ in 1897, first described vocal-cord paralysis associated with heart disease, his 2 cases occurring in mitral stenosis. At autopsy an enlarged auricle was reported to have caused compression of the recurrent laryngeal nerve against the aorta. In 1904 Alexander² was the first to advance the theory that the pulmonary artery by its own enlargement, or indirectly by enlargement of the left auricle, is pressed against the nerve and the arch of the aorta. Frischauer,³ in 1905, found the nerve compressed between the aorta and left pulmonary artery by the pressure of a dilated left auricle and pulmonary vein. Fetterolf and Norris⁴ (1911) reviewed 37 cases and, after careful anatomic studies of frozen specimens, concluded that dilatation of the left auricle caused the left pulmonary vein to press against the pulmonary artery, the latter in turn being forced against the aorta. It was their belief that the nerve paralysis was due to actual compression between the left pulmonary artery and aorta or ligamentum arteriosum. Kraus⁵ suggested that in mitral stenosis the right ventricular dilatation caused a displacement of the heart to the right, with consequent dragging on the aortic ligament and resultant stretching and paralysis of the nerve. Guttman and Neuhof⁶

observed that the nerve may also be compressed and incorporated between bands of pericardial and mediastinal adhesions, this occurred in a case of theirs in which pericarditis was present. Careful anatomic studies by Dolowitz and Lewis⁷ demonstrated that the lymph nodes in the triangle formed by the pulmonary artery, aortic arch and ligamentum arteriosum might effectively compress the left recurrent laryngeal nerve when accompanied by cardiac hypertrophy or pulmonary-artery engorgement, or both. Other authors have suggested that the cicatrization occurring in sclerosis, thrombosis and atheromas of the pulmonary artery may be contributing factors. Emphasis has been placed upon dilatation of the pulmonary vessels which may be apparent by fluoroscopy but may not be observed at autopsy.

The paralysis may occur at any time and is manifested by changes in the voice, which becomes hoarse and indistinct. The patient may be able to speak in a whisper. Laryngoscopy shows anything from a complete paralysis to sluggish movement of the vocal cord on the left side. The nerve is usually affected slowly by the gradual enlargement of the surrounding structures without marked accompanying cardiac symptoms, or it may be paralyzed rather suddenly during a sudden decompensation in a chronic case. Not infrequently there are relapses or recurrences of the paralysis of the left recurrent laryngeal nerve. In some cases the voice disturbance may be the first symptom that leads the patient to consult a physician. If the pressure has not been too severe or too prolonged, function will return with the removal of the cause. The prognosis in these cases is that of nerve injury from pressure in general.

CASE REPORTS

CASE 1. G. G. (A. H. 74076), a 61-year-old widowed sand blaster, came to the Outpatient Clinic of the Albany Hospital

*Assistant in medicine, Albany Medical College; assistant resident in medicine Albany Hospital.

history revealed only that a sister had died of pulmonary tuberculosis in 1912. The patient was not a heavy smoker and did not drink inordinately.

Physical examination disclosed a middle-aged man lying quietly in bed. He was moderately apprehensive. There was mild bulbar conjunctival injection. The peripheral vessels were tortuous, but not difficult to compress. The ocular fundi showed Grade I arteriosclerosis. The neck was supple. The chest was of an emphysematous type and the lung fields were clear. The heart sounds were very distant and difficult to hear. An arrhythmia was present that was interpreted as representing premature beats. The point of maximum impulse could not be palpated. No murmurs were heard. The abdomen was normal except for marked deep epigastric tenderness, pressure causing the lethargic patient to cry out. Peristalsis was readily heard. The extremities were normal. Neurologic examination was negative except for mild disorientation.

The temperature was 102°F, the pulse rate 64, and the respirations 22, the blood pressure in both arms was 120/78. Examination of the blood disclosed a red-cell count of 5,200,000, with a hemoglobin of 16.8 gm., and a white-cell count of 4200, with 61 per cent neutrophils and 39 per cent lymphocytes. Urinalysis was negative. The serum amylase was 147 units, the cephalin flocculation test was + in 24 and +++ in 48 hours. The sedimentation rate (Wintrobe method) was 8 mm. per hour. The blood urea nitrogen was 14.8 mg. per 100 cc. The cerebrospinal fluid contained 516 leukocytes per cubic millimeter, with 185 polymorphonuclear cells and 331 lymphocytes, a total protein of 63.3 mg., glucose of 63.3 mg. and chloride of 736.7 mg. per 100 cc.

A teleroentgenogram was normal, but electrocardiograms manifested a decreased voltage of the QRS complexes, frequent auricular premature beats and sinoauricular block with ventricular escape beats. The T wave in Lead 3 was of greater amplitude than that of Lead 1, which was considered probably abnormal, but the concomitant amplitude discrepancy in the QRS complexes of the same leads makes this equivocal. The very small R wave with a deep S wave in Lead CF₄ is also abnormal suggesting some myocardial disturbance in the lateral wall of the left ventricle.

The patient was treated with ordinary analgesics, and a tentative diagnosis was made of central-nervous-system viral infection of unknown type. Five days after admission a characteristic acute parotitis on the right, with swelling, tenderness and inflamed right parotid-duct orifice, rapidly developed. The serum amylase at this time was 22.4 units.

The subsequent course was uneventful, the temperature falling by lysis in 8 days, with a gradual disappearance of symptoms. Cerebrospinal-fluid studies later revealed a gradual return to normal limits. Cultures of blood and cerebrospinal fluid were repeatedly negative. Sixteen days later an electrocardiogram disclosed none of the conduction defects noted above, although the discrepancy in the T waves in Leads 1 and 3 and the absence of a normal R wave in Lead CF₄ persisted. The patient was discharged 37 days after admission, when he felt perfectly well. He was seen 6 months later and was still well, with no suggestion of sequelae.

DISCUSSION

Unequivocal meningoencephalitis, as diagnosed by clinical and laboratory methods, was present in this case. A diagnosis of acute pancreatitis was thought justified in view of the sudden onset of violent nausea and vomiting persisting for forty-eight hours, the definite though subjective evidence of marked tenderness deep in the epigastrium and the sense of expanding epigastric pressure that did not radiate. The change in serum amylase may or may not have been significant. The patient had marked apprehension and orthopneic symptoms, which were followed by two episodes of sudden, unpredictable syncope with unconsciousness lasting one or two minutes, the electrocardiographic changes of decreased QRS complex, premature auricular contractions and ventricular escape suggested some

interference with origin of the auricular impulse or poor auriculoventricular conduction. He also had dyspnea on the day of his admission while engaged in refrigerator-repair work, not a strenuous occupation. All this suggests imminent left-ventricle failure, as well as some degree of transient auriculoventricular or sinoauricular heart block. It was believed that these findings justified a diagnosis of myocarditis.

An etiologic diagnosis was not reached until the patient later developed acute right parotitis. Mumps can so readily explain the entire chain of events despite the unusual sequence that the patient was considered to have had the mumps virus, which had manifested its pathologic changes in the central nervous system, pancreas, heart and right parotid gland. The widespread distribution suggested blood-stream spread.

The case presented and the review of the literature strongly suggest that mumps myocarditis goes frequently unrecognized and usually manifests itself in a subclinical form. The importance of its recognition is that with the knowledge of its presence, one is more inclined to prolong the convalescence to prevent the occurrence of myocardial residua in the event of extensive involvement. Apparently, there are no residua, and the process is completely reversible in the vast majority of cases, though reversal may be delayed by failure to recognize its presence. It seems worth while to suggest the use of the complement-fixation test and the intradermal skin test of Enders,⁵ as a diagnostic aid in an obscure myocarditis. The PR-interval changes discussed in the literature make the specificity of such changes in rheumatic fever a matter of conjecture. Wendkos and Noll⁶ showed that the PR-interval prolongation of mumps myocarditis is shortened by atropine sulfate, as is the prolonged PR interval of acute rheumatic fever. The non-specific nature of this electrocardiographic change should be appreciated. Though a PR interval may be within usual normal limits for the age of a patient, one should keep in mind that a tracing taken after recovery may show a much shorter PR interval, which is actually normal for the particular patient.

Rosenberg⁷ has stressed the fact that mumps myocarditis is probably not rare and has ably presented the implications of work done thus far and the importance of further study. Inasmuch as mumps is frequently not reported, a statistical study is difficult to accomplish and electrocardiographic study in all acute infectious diseases might well prove fruitful whenever such a program is feasible.

SUMMARY

A case in which mumps was complicated by myocarditis, meningoencephalitis and pancreatitis is presented.

TORSION OF THE NORMAL FALLOPIAN TUBE COMPLICATING PREGNANCY*

Report of a Case

RENWICK K CALDWELL, M D †

NORTHFIELD, VERMONT

BECAUSE torsion of the normal fallopian tube is a rare complication of pregnancy, the following case is added to those already on record

Mrs J B, a 23-year-old primigravida, was admitted to the hospital on July 30, 1948. Eleven days previously she experienced her first attack of pain in the right anterior portion of the abdomen. This pain began without a known precipitating cause, had no localizing signs or symptoms and disappeared when the patient remained in the upright position for 20 minutes. After this episode and until 2 days before admission, the pain recurred daily, appearing occasionally in the right flank as well as in the right anterior portion of the abdomen. Three days before admission the patient noted intermittent urinary frequency. White cells were found in the sediment on microscopical examination of the urine. After a day without discomfort and on the day preceding admission the pain reached its maximum severity, and an area of right-lower-quadrant tenderness was noted for the first time.

The patient's last menstrual period had begun on February 6, and the estimated date of confinement was November 13. Except for morning sickness controlled by intravenous injections of thiamine hydrochloride and pyridoxine hydrochloride, the pregnancy had been uneventful. The past and family histories were noncontributory.

Examination of the blood disclosed a white-cell count of 11,600. Except for 28 per cent immature neutrophils, the differential count was normal.

Because of the urinary frequency and pyuria cystoscopy was done. There were no abnormal findings. After the cystoscopy, and because of the persistence of the right-lower-quadrant pain, a laparotomy was performed.

Under general anesthesia the abdomen was opened through a right-rectus incision. The uterus was enlarged to a size consistent with a 5 or 6 months' pregnancy. The right ovary was located, and beneath it was a dark mass roughly 4 by 3 cm. This mass was elevated and, by untwisting, was found to consist of the terminal two thirds of the right fallopian tube, which then resumed its normal position. The demarcation between the normal and hemorrhagic areas of the fallopian tube was definite, and the nonviable portion of the tube was removed with ease. To avoid premature termination of the pregnancy, manipulation of the uterus was kept at a minimum. The appendix, which appeared normal, was not removed.

The immediate postoperative course was marked by a gradual diminution of the pain. Discharge from the hospital was delayed by slow healing of the skin wound.

Since leaving the hospital the patient has been free of pain, and the pregnancy has progressed normally.

On pathological examination† the specimen consisted of a dark-brown mass of tissue 4 by 3 by 2 cm. On cut section

there was a soft, red-brown and brown surface with one cystic space approximately 1 cm in diameter. On microscopical examination the tube, lumen and wall were filled with red blood cells. The epithelium was largely destroyed, and that which remained was low columnar. It appeared that the congestion and hematosalpinx followed the torsion of the tube.

The rarity of torsion of the normal fallopian tube during pregnancy has been noted. McKerrow¹ reported such a case with involvement of the right tube, and Sheldon² discussed a case in which both the right tube and ovary had undergone complete torsion and become gangrenous. Two additional articles have appeared in recent years in foreign-language journals. Torsion of the tube after hematosalpinx is somewhat more common, and Savage,³ in 1936, reported such a case and gathered 13 similar cases from the literature.

Because of the infrequent occurrence of this complication, the diagnosis is not made until operation. The majority of cases of torsion of the fallopian tube, normal or otherwise, during pregnancy have involved the right tube. In these cases the preoperative diagnosis of acute appendicitis was frequent and logical. In McKerrow's¹ case and that reported above there were findings suggestive of genitourinary disease, but in both cases cystoscopic examination was negative. Ovarian cyst with twisted pedicle, ectopic pregnancy in the fallopian tube and hydrosalpinx are other possible preoperative diagnoses.

SUMMARY

An additional case of torsion of the normal fallopian tube during pregnancy is reported. This rare complication is diagnosed correctly by laparotomy.

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*From the Green Mountain Clinic.

†Physician Green Mountain Clinic attending physician Mayo Memorial Hospital.

‡Performed at Dartmouth Medical School Hanover New Hampshire.

on May 5, 1948, with signs and symptoms of severe congestive failure. For 7 months prior to admission there had been progressive weakness, hoarseness, dyspnea, orthopnea, ankle edema, palpitation and precordial distress. During this time there were also episodes of left-sided chest pain, associated with a cough productive of small amounts of frothy blood-streaked sputum.

Aside from appendicitis and gonorrhea the past history was not significant. The family history was noncontributory.

Physical examination revealed the patient to be markedly dyspneic and orthopneic, with some cyanosis of the lips and nail beds. The fundi showed arteriovenous nicking and tortuosity and narrowing of the arteries. The neck veins were distended. Percussion of the chest revealed dullness over the left base posteriorly with absent breath sounds over this area. Moist rales were heard throughout both lung fields. On percussion the border of cardiac dullness extended to the left anterior axillary line, and the point of maximal impulse was located in the sixth intercostal space. The rhythm was totally irregular, and the sounds were of poor quality. No murmurs were heard. The abdomen was slightly distended, and the edge of the liver, which was firm and smooth, was palpated 4 cm below the right costal margin. There was pitting edema of the lower extremities extending above the knees.

The temperature was 100.8°F, the pulse 106, and the respirations 28. The blood pressure was 250/140.

The urine was normal. Examination of the blood disclosed a hemoglobin of 14 gm, and a white-cell count of 12,000, with 94 per cent neutrophils. The fasting blood sugar was 123 mg, and the nonprotein nitrogen 46 mg per 100 cc. The blood Wassermann reaction was negative.

A roentgenogram of the chest showed the heart to be enlarged. There was diminished transmission of rays through the left side of the chest, with displacement of the cardiac shadow to the right, suggesting effusion.

An electrocardiogram revealed auricular fibrillation and left-axis deviation, with left ventricular hypertrophy and strain. There was also evidence of myocardial damage.

A clinical diagnosis of hypertensive heart disease, with decompensation, auricular fibrillation and multiple pulmonary emboli with pleural effusion, was made.

The patient improved after treatment with bed rest, oxygen, diuretics, 1-gm sodium diet, digitalis and dicumarol. Thoracentesis was performed twice, and neither the hemorrhagic pleural fluid nor the sputum showed tubercle bacilli or tumor cells.

On the 15th hospital day laryngoscopy demonstrated sluggish movement of the left vocal cord. As the patient continued to improve the heart decreased in size, and on the 31st hospital day he was discharged. His hoarseness had improved, and when he was seen again in the Medical Outpatient Clinic 3 months later it had cleared completely.

CASE 2. M S (A H 48565), a 50-year-old housewife, came to the Albany Hospital for the first time on July 15, 1938, with signs and symptoms of severe congestive failure. For 6 months prior to admission there had been progressive dyspnea, ankle edema, orthopnea and weakness.

The past history was significant only in that she had had hypertension since her third pregnancy in 1931. The family history was noncontributory.

Physical examination showed the patient to be in severe congestive failure with a blood pressure of 240/120. After treatment and study a clinical diagnosis of hypertensive heart disease with decompensation and auricular fibrillation was made. She was discharged improved on the 20th hospital day to be followed in the Outpatient Clinic.

Since that first admission she has been hospitalized ten times for similar episodes of decompensation. Of particular interest has been the gradual increase in the size of the heart, which on x-ray study has shown an increase of 7 cm within the past 4 years.

Hoarseness developed rather suddenly on October 11, 1945, and has persisted to date. Laryngoscopy showed complete paralysis of the left vocal cord. In view of the long-standing

decompensation with marked cardiac enlargement the prognosis regarding the hoarseness is poor.

DISCUSSION

These are 2 typical cases of vocal-cord paralysis associated with heart disease. When a patient with a cardiac lesion complains of hoarseness and laryngoscopy is confirmatory, paralysis of the left recurrent laryngeal nerve must be suspected as being due to pressure on the nerve. With the institution of proper therapy, if successful, the paralysis disappears. The condition in Case 1 responded satisfactorily to therapy, in Case 2 hoarseness appeared suddenly, and with the progressive cardiac hypertrophy and dilatation in spite of therapy, the paralysis is now complete and permanent.

SUMMARY

Left vocal-cord paralysis is frequently observed with various forms of intrathoracic disease. A variety of cardiac lesions may also produce this syndrome. The theories of the mechanism involved are summarized.

Two cases of hypertensive heart disease with vocal-cord paralysis are presented.

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These treatment schedules are technically more difficult to administer, and the likelihood of reactions is inescapably higher. The co-operation of patients would obviously be difficult to obtain in many cases.

Arsenotherapy

Reports of intensive treatment of early syphilis with triweekly injections of mapharsen and concomitant weekly injections of bismuth continue to appear.⁵⁷⁻⁵⁸ These are follow-up studies of rapid treatment schedules that were in the course of development just prior to the advent of penicillin. From nine to fifteen weeks were required to complete these schedules. The results were good, with as high as 90 per cent satisfactory cumulative percentage by the end of three years. Serious reactions were infrequent compared to more intensive massive-therapy schedules, but in comparison to penicillin the reaction rate and severity were high.

Relapse vs. Reinfection

The remarkably successful use of penicillin in the treatment of early syphilis has been clouded to some extent by the difficulty in ascertaining the true percentage of relapses as contrasted to reinfection. The relative ease of cure that is now available is bound to create a greater degree of carelessness among many less responsible citizens. The symptoms of an early infection can be relieved more quickly than the common cold in a large percentage of cases. With slight exaggeration, it might be said that a habitual offender could acquire new infections almost faster than each preceding one was cured. It is thus obvious that differentiating failure of treatment, or syphilitic relapse, and a true reinfection may present the most complicated of problems. For the benefit of absolute accuracy, the rates of failure with treatment as efficient as penicillin should therefore include all patients in a given series who require retreatment within at least the first few months following the initial course of therapy. Rigid criteria for the determination of relapse and reinfection, as practiced in the past, have of necessity been abandoned. Many such differentiations now appear to rest on clinical impressions rather than on certainty. One new set of criteria has been presented that seems to deserve consideration.⁵⁹ It is held that the diagnosis of syphilitic reinfection in persons previously treated for syphilis should require clinical evidence of a second infection preceding the serologic evidence. It is further stated that the response to a second treatment course should be similar both clinically and serologically to that seen with the previous infection. Epidemiologic evidence is held to be of distinct value. Exposure to a person with known infectious syphilitic lesions, followed by the development of the infection after a proper incubation period in the patient under consideration,

is strong evidence of reinfection. Obviously the primary lesion should be a darkfield-positive chancre. The treatment of the preceding infectious episode must certainly have been adequate, or it would point to the likelihood of relapse. A period of seronegativity between the two infectious episodes is highly desirable in the effort to prove reinfection.

LATE SYPHILIS

Less effort has been expended in the treatment of late syphilis with penicillin than any other stage of the disease. The results in late latent syphilis have been discouraging. In cardiovascular disease, the effects of penicillin are questionable. In other active phases of late syphilis, there is more encouragement, but it seems highly questionable whether penicillin alone should be depended upon.

In most forms of late active syphilis it is imperative to avoid Herxheimer reactions. This is particularly vital in visceral disease. Cole⁶⁰ has advocated that all patients with late syphilis receive a course of heavy metal (bismuth) in addition to potassium iodide preceding penicillin therapy to obviate the danger of reactions. This is excellent advice and might well be carried a step farther. A diagnosis of late latent syphilis may be correct as far as it is possible to determine, and yet the patient may have a concealed active lesion. Thus, it is equally appropriate to give a latent case the chemotherapy preceding penicillin.

There is fairly general agreement that late latent syphilis is a field in which penicillin treatment is far from proved in value.⁷⁶⁻⁹³ It is not yet known whether penicillin may be of preventive value in latent syphilis, although the efficacy of traditional chemotherapy has long been accepted in that respect. It will take many years to determine this point. Certainly, one should not rely on penicillin alone in either latent or active late syphilis until far more has been accomplished with this mode of treatment. The suggested dosage schedules in many cases are similar to those recommended for neurosyphilis.

In late cutaneous syphilis moderate doses of penicillin have been striking in their effect.⁷⁶ Not all late gummatous syphilis is responsive to penicillin.⁹⁴ Syphilis of the bone is known to respond satisfactorily to penicillin therapy in most cases.⁷⁶⁻⁹⁵ A word of caution should be interjected regarding these so-called benign forms of late syphilis. Their clinical response to any form of therapy may seem satisfactory, but serologic response is often exceedingly slow and sometimes apparently nonexistent. It must be constantly borne in mind that syphilis is a systemic disease and reliance cannot be placed upon the behavior of any one symptomatic phase of the disorder.

A survey of 550 patients with late syphilis treated by penicillin has appeared from the Johns Hopkins

MEDICAL PROGRESS

SYPHILIS* (Concluded)

G MARSHALL CRAWFORD, M D †

BROOKLINE, MASSACHUSETTS

Serologic Response

A prolonged follow-up study of the pattern of serologic response after penicillin therapy for early syphilis is of utmost importance. A monthly quantitative test is desirable in all cases and should be performed for probably not less than a year. The quantitative determination of reagin titer at monthly intervals will enable the practicing physician correctly to assay the response to treatment and should warn him of an impending relapse before it becomes clinically manifest. In early syphilis adequate therapy with penicillin will usually reverse positive serologic tests to negative in about six months.⁷⁴ Some patients, especially in the late secondary or early latent stage, may require much longer than six months to become seronegative. Small amounts of reagin in the blood for longer than six months after treatment do not necessarily require retreatment. Conversely, a consistent slow rise in titer should indicate the need for repetition of a course of therapy. If the serum reagin titer does not show a steady and progressive drop during the first six months, another indication for retreatment is presented. These statements apply strictly to early syphilis.

Quantitative serologic examinations in the follow-up study of penicillin-treated syphilis not only are a guide in response to treatment and an aid in predicting an impending relapse but also may serve as a helpful means of differentiating serologic relapse and reinfection.⁸⁰ In relapses there is frequently a sudden sharp increase in serologic titer, after an apparent response to treatment that has not resulted in a completely negative test. Patients who become reinfected have usually attained and maintained complete serum negativity followed by the development of a new primary lesion at a new site with the development of seropositive reaction shortly thereafter. A new chancre should certainly be darkfield positive.

A comparison of the serologic response following penicillin therapy with that following previously established methods has been used to gauge therapeutic efficacy as shown by serologic cure.⁸¹ Two hundred and eight patients with untreated primary or secondary syphilis were hospitalized and treated

with three different schedules of penicillin therapy. The serologic response in these cases was compared with data from a similar series of patients who had been given arsenical treatment. The rate of fall of serum reagin was observed to be comparable in each group, although in some classifications the penicillin response was a little slower. If this is correct, it merely illustrates that the actual efficiency of penicillin is not remarkably greater than that of arsenic, when assayed from this one standpoint.

Combined Therapy

Numerous schemes combining penicillin with bismuth, arsenic, fever and so forth have been studied in a search for a possible ideal adjuvant to penicillin. So far there is no report of greater efficiency or anything like as low a rate of reactions as that seen with penicillin alone. One series of 1350 patients with early syphilis received a combination of mapharsen and penicillin.⁸² After six months' follow-up study, 83.6 per cent were seronegative. The incidence of reactions was high. A small series of cases treated with bismuth and penicillin showed no better results than a control group receiving only penicillin.⁸³ One report is actually pessimistic about penicillin.⁸⁴ Another analysis compares groups of patients treated biweekly or triweekly with mapharsen or neoarsphenamine, massive arsenotherapy, penicillin alone and penicillin combined with arsenoxide and bismuth.⁸⁵ The most rapid response was obtained with arsenoxide twice weekly. The combined penicillin-chemotherapy group was seven weeks slower in serologic response, and the failure rate was approximately 17 per cent.

The combination of penicillin and fever therapy in early syphilis has been studied from the standpoint of increasing the favorable effects of penicillin in a given dosage and also the possibility of shortening penicillin therapy without the loss of efficiency.⁸⁶ The maximum dosage was 1,200,000 units of penicillin over a period of seven and a half days, in addition to three sessions of physically induced fever. The failure rate in this group was a little more than a third lower than that in a comparable group receiving the same amount of penicillin alone, but the result was distinctly less favorable than that after more satisfactory penicillin dosage without adjuvants. Attempts to shorten the penicillin-fever therapy to thirty hours were unsuccessful.

*From the Department of Dermatology and Syphilology, Harvard Medical School, and the Massachusetts General Hospital.

†Instructor in dermatology, Harvard Medical School, dermatologist, Massachusetts General Hospital.

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Hospital and casts a decidedly questionable light on the value of this treatment.⁹¹ Treatment failures are said to occur in the form of drug resistance, clinical progression, recurrence of lesions after an initially favorable response and the subsequent development of new manifestations of syphilis elsewhere in the body. A significant number of cases are presented, suggesting that penicillin may prove less efficacious in the later stages of syphilitic infection than during the more acute early phases of the disease. It is obvious that a great deal of further observation is required before penicillin may be considered lastingly efficacious in late syphilis. Perhaps this agent should be regarded as an adjuvant to traditional chemotherapy in some forms of late syphilis, rather than vice versa as considered in early stages of the disease.

CARDIOVASCULAR SYPHILIS

Several general reviews of the problem of cardiovascular syphilis and additional studies of special phases have been reported during the past year.

It is estimated that 10 per cent of all cases of early syphilis develop cardiovascular involvement.⁹² This should be preventable by adequate therapy early in the disease. A survey of 177 cases of cardiovascular syphilis was undertaken to determine how many patients had received adequate treatment either during the early stages of their syphilis or during the latent period, and to determine the effect of treatment on advanced cases of syphilitic aortitis.⁹⁶ Exceedingly low percentages of all the types of cardiovascular syphilis were found to have had anything like adequate treatment in the early stages of the disease. Some of these patients were under observation for ten years or more. The authors were unable to determine definitely what effect, if any, specific antisyphilitic treatment had had upon prolonging the life of these patients. It was stated that treatment of uncomplicated syphilitic aortitis will often prevent the development of serious cardiovascular complications. Once aortic insufficiency or aneurysm has developed, it is questionable whether antisyphilitic treatment can arrest the process, and it must certainly be used with great caution. One reviewer states that syphilis of the aorta and its complications comprise 13 to 15 per cent of all cardiac diseases found at autopsy.⁹⁷ Another presentation discusses a study of 43 patients with syphilitic aortic insufficiency who had received standard chemotherapy and were followed from two to sixteen years.⁹⁸ The data indicated that there may be an asymptomatic phase of from two to ten years followed by a symptomatic period, which may last an additional two to fourteen years. Cardiac failure was found to be as readily controlled with digitalis and mercurial diuretics as in other types of heart disease. An analysis of 59 cases of aortic aneurysm is also available.⁹⁹ Only 25 per cent of these patients gave a history of a

chancre. None were considered to have received adequate treatment. No difference was found in the appearance of the lesion in treated and untreated cases.

Therapy

All writers on this topic are in agreement that in the presence of cardiovascular syphilis, patients should be prepared with bismuth injections to prevent Herxheimer reactions.^{71 71 97 100} Individualization of the patient is imperative. Cardiac therapy should be the same as that for heart disease from other causes. Antisyphilitic therapy should be stopped if the patient is not improving or is growing worse, and treatment should be directed to the heart condition until cardiac signs and symptoms improve. Antisyphilitic therapy should invariably be withheld in the presence of cardiac failure. In the early days of penicillin there was considerable hesitance on the part of cardiologists to use this antibiotic in the treatment of cardiovascular syphilis. Experience has proved penicillin less dangerous to these patients than was at first believed. Initial doses as low as a few hundred units are advocated. One series comprised 28 patients with syphilitic aortic insufficiency and 8 with thoracic aortic aneurysm.¹⁰¹ Total dosage varied from 2,000,000 to 15,000,000 units, and there was an absence of severe reactions throughout. Five patients had fever within the first sixteen hours of treatment, and 2 with long-standing angina at rest had attacks of usual severity and frequency during and subsequent to administration of penicillin. In no case was the treatment schedule interrupted. There was no significant difference in the incidence of reactions or cardiovascular symptoms in the patients who received small initial doses as compared with those who received 25,000 to 100,000 units for their first dose. The average total of penicillin therapy advocated has been 6,000,000 units in from ten to fifteen days.^{71 99}

One author states that there is too little knowledge regarding the treatment of cardiovascular syphilis with penicillin for this subject to be discussed intelligently.⁹⁷ He believes that the weight of evidence indicates that syphilitic aortitis will not be permanently arrested unless arsenical therapy is included in any course of thorough and prolonged treatment. The arsenical agent of choice is stated to be arsenoxide (mapharsen, chlorarsen or similar preparations). It remains to be seen whether this opinion is correct as further work with penicillin progresses. It may well be ten to twenty years before the question of penicillin therapy in complicated syphilitic aortitis can be settled.

NEUROSYPHILIS

Next to early syphilis, more effort has been expended in the study of penicillin therapy of neurosyphilis than any other phase of the disease.

Results with penicillin have not been so dramatic as in early syphilis. The most outstanding effect has been favorable changes in the spinal fluid, particularly the cell count. There is considerable controversy regarding the question of using penicillin alone versus penicillin combined with fever therapy or other adjuvants in the treatment of neurosyphilis.

One of the most easily recognized objective findings in neurosyphilis and one upon which much reliance is placed is inequality of the pupils. The incidence of anisocoria was found to be nearly 17 per cent in a study of 500 normal subjects¹⁰². In $\frac{1}{4}$ per cent of this group there was a pronounced difference in pupillary size. Inequality of the palpebral fissures was even more frequent. Imbalance of sympathetic innervation and differences in refractive errors are considered to be possible explanations for at least some cases of anisocoria. It is obvious that too much reliance cannot be placed upon this one objective finding in an attempt to establish a diagnosis of neurosyphilis.

In a study of 54 patients with syphilitic primary optic atrophy, it was found that loss of vision was the first manifestation of neurosyphilis in 63 per cent¹⁰³. The optic atrophy was generally found to be accompanied by strongly positive cerebrospinal-fluid findings unless antisyphilitic treatment had been started. A majority of the cases exhibited the tabetic type of neurosyphilis. Fever therapy was found to be superior to chemotherapy in this series and the prognosis was not too unfavorable, provided that treatment was begun before useful vision had been lost. Of 16 patients given fever therapy in addition to chemotherapy, only 2 (13 per cent) were blind on follow-up examination two years or more after treatment. Another study led to the advocacy of malarial therapy aided by concomitant and subsequent courses of penicillin, each course consisting of the administration of at least 5,000,000 units¹⁰⁴. This work comprised a study of anatomic material of 12 cases of syphilitic primary optic atrophy, in 2 of which death had occurred at a time when the atrophy was confined to one eye. It was found that by the time demyelination of the nerve fibers had progressed to complete degeneration in one optic nerve, there was already present in the normal nerve a syphilitic inflammatory exudate that ultimately led to atrophy of the second nerve. It was stated that optochiasmatic arachnoiditis has nothing to do with the atrophy of the optic nerves.

In nerve deafness due to syphilis, penicillin has been found to be fully as effective as the older methods of therapy, only 13 patients with syphilitic deafness were studied, but this complication is not a common one¹⁰⁵. Patients with acute syphilitic meningitis and deafness responded rather well. In late syphilis with deafness of longer duration, the response to penicillin therapy was less favorable and considerably delayed. Some patients showed

no improvement, but there was no progression. One case of late congenital syphilis continued to show progressive loss of hearing. There was no evidence that penicillin has an unfavorable effect on hearing.

In severe, poorly regulated diabetes mellitus of long duration there may be neurologic changes that closely mimic tabes dorsalis (diabetic pseudotabes). Sensory disturbances, evidences of posterior-column damage, areflexia and a predilection for the lower extremities are common to both conditions. A group of 17 cases of neuropathic arthropathy of the feet associated with diabetes mellitus has been reported¹⁰⁶. These patients had destruction of the tarsal or metatarsal bones that was roentgenologically similar to that observed in Charcot joints. It was pointed out that the Charcot joint is more likely to exhibit an acute onset of fluid with swelling of the extremity and is usually painful during the acute stage and that new bone formation can frequently be demonstrated in the Charcot joint, whereas these findings are seldom notable in the diabetic neuropathic foot. The Charcot joint is relatively less frequent in the foot than in other joints, whereas feet are the most common site of diabetic neuropathy. Two additional cases have been reported in which neurogenic arthropathy of the Charcot type in severe diabetes of long standing was accompanied by the development of cord bladder¹⁰⁷. Here again are examples of the occurrence of lesions commonly designated as evidence of neurosyphilis in nonsyphilitic persons. Nevertheless, it is necessary to exert every effort to rule out neurosyphilis, regardless of negative serologic tests for syphilis, by careful clinical examination and lumbar puncture in patients such as those described. In other words, diabetic neuropathy should not be allowed to mask an actual case of neurosyphilis.

There is general agreement among syphilologists that spinal-fluid findings are of primary import in the diagnosis and management of neurosyphilis. It is not agreed, however, what constitutes normal standards for some of the tests done on the spinal fluid or what the different tests signify. There are four that should certainly be considered obligatory in all cases: cell count, total protein, colloidal gold and complement-fixation test. No single item will give complete information on the process involving the central-nervous system. An evaluation of spinal-fluid tests, based on thousands of examinations, has appeared from Bellevue Hospital¹⁰⁸. The presence of 3 cells per cubic millimeter of spinal fluid is regarded as normal, 3 to 5 cells are considered to represent borderline values, and more than 5 cells are held to be definitely pathologic. The cell count should be a reliable indication of the activity of the process. The total protein determination in association with the cell count is a further indication of activity, normal values for total protein in the spinal fluid are stated to range from 10 to 30 mg

per 100 cc. The colloidal gold test in its qualitative aspect gives a clue to the prevalent type of central-nervous-system tissue involvement, and its quantitative values offer an indication of the trend of the process. It is stated that in addition to a qualitative trend, a quantitative value may be obtained by addition of the ten figures of the colloidal gold test, a comparison of results is afforded with spinal fluids examined at various periods in the follow-up study of treated patients. The complement-fixation test should signify the specific nature of the syphilitic disease. Quantitative reagin readings, together with the other tests, provide additional information about whether the process in the central nervous system is progressing or abating or has been checked and thereby permit more intelligent management of a patient with neurosyphilis. Quantitatively determined spinal-fluid examinations have not been in general usage, but their value is being more widely recognized.¹⁰⁹

Therapy with Penicillin Alone

Stokes and his associates¹¹⁰ have presented a three-year study of penicillin alone in the treatment of neurosyphilis at the University of Pennsylvania, 361 patients were followed for periods of three months to three years. Of the total number of patients followed, spinal fluids were normal or nearly normal in over half, 74 per cent were markedly improved. Improvement in the spinal fluid appeared to level off in approximately 70 per cent of cases by the second year. Additional courses of penicillin produced little further improvement in most cases. In symptomatic neurosyphilis a single course of 9,600,000 units in aqueous solution given at two-hour intervals during a period of ten to fifteen days is under study. Asymptomatic neurosyphilis is being treated with penicillin in oil and wax. A comparison of the results of penicillin therapy and malaria suggested that penicillin alone is equal to or better than malaria in the management of neurosyphilis. In *tabes dorsalis*, the results with penicillin were considered to be twice as good after the second year as with malaria. Low initial doses (500 units) of penicillin, increasing to full dosage by the fifth day, were stressed to avoid therapeutic shock. A still greater percentage of satisfactory results is reported in the treatment of neurosyphilis with penicillin alone at Bellevue Hospital.¹¹¹⁻¹¹⁴ The total dose varied from 2,000,000 to 9,000,000 units, and the injections varied from 75 to 200. There were 301 patients with active neurosyphilis who were treated and followed from six to forty-five months, of which only 11 per cent had to be retreated. Of the original failures over half responded well to a second treatment with larger total doses of penicillin alone. The evaluation of therapy in this group of patients was based almost entirely on the results of repeated spinal-fluid examinations.

Another series of 141 patients received 4,000,000 units of penicillin, and the neurosyphilitic process was considered arrested in approximately 85 per cent of the cases.¹¹⁵ Early neurosyphilis responded more satisfactorily, and in cases of this type the results were as good as those obtained from fever therapy. It was concluded that in late symptomatic neurosyphilis, fever therapy was the treatment of choice. A schedule of 6,000,000 units of aqueous penicillin in eighteen days is considered satisfactory by another author.⁷⁴ He believes that at least 90 per cent of neurosyphilis will be arrested by that amount of penicillin and states that 9,000,000 to 12,000,000 units of penicillin in oil and wax over a period of eighteen to twenty days will probably give comparable results.

To evaluate the effect of previous chemotherapy on the results of penicillin treatment of neurosyphilis, clinical and serologic observations were made in 45 patients followed for one or two years after subsequent penicillin treatment.¹¹⁶ Total dosages of 8,000,000 to 12,000,000 units were given for eighteen to twenty-one days. Penicillin was considered superior or equal to malaria in the treatment of all phases of neurosyphilis with the possible exception of paresis. Mixed opinions regarding the use of penicillin alone versus penicillin and malaria in the treatment of neurosyphilis are expressed by other authors.¹¹⁷⁻¹¹⁹ It is indicated in general that the more advanced and serious forms of neurosyphilis often require repeated courses of penicillin or penicillin and fever combinations to achieve success.

An analysis of the blood serologic tests in 213 cases of late symptomatic neurosyphilis treated with various amounts of penicillin and observed for periods of six to twenty-four months or more after treatment indicated that less than 10 per cent of the patients attained complete serologic reversal.¹²⁰ Increased penicillin dosage or repetition of the course did not increase the percentage of serologic reversal. These findings are in agreement with the generally observed fact that penicillin seems to have little effect in reversing the positive blood serologic tests to negative in late neurosyphilis.

Intrathecal administration of penicillin has been advocated from a few sources but has not received general approval. One series of 179 cases has been reported, but the results are not superior to those in most of the aforementioned penicillin schedules with intramuscular injection.¹²¹ Reactions to intrathecal penicillin were stated to be about the same as those following routine lumbar puncture and less than those following Swift-Ellis treatments or malaria. Serious toxic effects have also been reported, however, and there is certainly little or no evidence that intrathecal administration is of greater therapeutic value in neurosyphilis than intramuscular injections.^{119, 122}

Combination Therapy

A number of authors reporting studies of varied methods of therapy of neurosyphilis state that the combination of penicillin and fever therapy is the treatment of choice in neurosyphilis, especially in the later symptomatic varieties.^{71 76 123} Assorted doses of from 4,000,000 to 20,000,000 units of penicillin are advocated in accordance with the type of neurosyphilis under consideration. Several methods of inducing fever have been employed, but malaria seems to be in more general use. There appears to be no striking difference in results whether the fever and penicillin are given concurrently or successively.

One study surveys progress as measured by the spinal-fluid examination among 458 cases of neurosyphilis treated with mechanical hyperthermy, malaria or penicillin in oil and wax with adjuvant chemotherapy.¹²⁴ All cases included in this group had a minimum observation period of six months. On the basis of failure rates, there were no significant differences among the three types of treatment in any diagnostic group. Penicillin appeared to eliminate activity in the spinal fluid more rapidly than the hyperthermy or malaria treatment. It should be remembered that this was not penicillin alone but with added chemotherapy. Various combinations of penicillin with fever or chemotherapy, or both, according to the type of neurosyphilis, are advocated elsewhere.¹¹⁹

A report from the Johns Hopkins Hospital on the treatment of 149 patients with neurosyphilis with penicillin alone or penicillin and malaria indicated that the patients in the latter group exhibited a more striking spinal-fluid response than those treated with penicillin alone.¹²⁵ The majority of patients had advanced neurosyphilis with pronounced spinal-fluid changes. Another series of 118 cases of neurosyphilis was managed in a similar fashion.¹²⁶ The combined penicillin and malaria therapy was generally administered to patients presenting the more serious clinical picture. The results for all types of central-nervous-system syphilis showed a distinctly superior clinical and spinal-fluid improvement after therapy in the patients given penicillin in combination with malaria as compared with those treated with penicillin alone.

The admittedly greater hazard of fever therapy, regardless of the method of induction, should largely discount its apparently somewhat greater value except in the more advanced and serious forms of neurosyphilis. Many patients in this category are so debilitated that fever therapy is out of the question and malaria therapy in particular has certain special contraindications. It is ardently hoped that improved methods of administration of penicillin will bring forth more evidence of its greater effectiveness in neurosyphilis.

Malaria therapy also presents a greater possibility of complications, studies in two series of neurosyphilitic patients gave laboratory evidence of impaired liver function in all or most of the patients.^{127 128} The degree of hepatomegaly could not be correlated with the severity of liver dysfunction. After termination of the malarial fever, most abnormalities gradually returned to normal. In no case was there evidence of permanent liver damage. Attention has again been called to the efficacy of thiobismol (sodium bismuth glycollate) in reducing the frequency of vivax malaria paroxysms without eliminating them completely.¹²⁹ This drug exerts an inhibitory effect upon half-grown parasites and thus facilitates temporary interruptions of malaria that may permit a full course of therapy without rapidly exhausting a patient who may be having daily febrile episodes. In quartan malaria, the use of thiobismol is less well understood, but it seems to be effective.

It is obvious that penicillin has a definite and established place in the treatment of neurosyphilis. Whether this antibiotic will prove sufficient by itself is yet to be determined. There is certainly evidence that in the more advanced forms of neurosyphilis, the combination of penicillin with fever and possibly with chemotherapy has a place. As stressed above, the preparation of patients with late syphilis with a series of bismuth treatments before any more dramatic form of therapy is given is an intelligent procedure. Neurosyphilis in its entirety falls within this category.

SYPHILIS IN PREGNANCY

The primary purpose of laws requiring a prenatal serologic test for syphilis is the protection of unborn children. Evaluation of these measures must therefore be in terms of the incidence of congenital syphilis. Many states have enacted such legislation, and a survey of the effectiveness of the law in 1 case was recently reported.¹³⁰ In a six-year period during the operation of this law, the population of the state showed a 34 per cent increase with a corresponding increase in the number of births, but the infant mortality for syphilis decreased from 0.50 to 0.15 per thousand live births. During the same interval the number of patients with congenital syphilis under one year of age reported to the state department of public health dropped from 163 to 74. This is a decrease in case rate from 1.60 to 0.54 per thousand live births. As reflected in these percentages, the effectiveness of the prenatal blood-test law is obvious.

The use of penicillin therapy for syphilis in pregnancy has been studied to a moderate extent, and the results appear most encouraging. A group of 287 cases of syphilis in pregnancy treated with penicillin has been reported from Bellevue Hospital.¹³¹ Among the patients treated only during pregnancy, there was an incidence of 2.8 per cent

per 100 cc. The colloidal gold test in its qualitative aspect gives a clue to the prevalent type of central-nervous-system tissue involvement, and its quantitative values offer an indication of the trend of the process. It is stated that in addition to a qualitative trend, a quantitative value may be obtained by addition of the ten figures of the colloidal gold test, a comparison of results is afforded with spinal fluids examined at various periods in the follow-up study of treated patients. The complement-fixation test should signify the specific nature of the syphilitic disease. Quantitative reagin readings, together with the other tests, provide additional information about whether the process in the central nervous system is progressing or abating or has been checked and thereby permit more intelligent management of a patient with neurosyphilis. Quantitatively determined spinal-fluid examinations have not been in general usage, but their value is being more widely recognized.¹⁰⁹

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A small number of patients will develop erythematous or erythematopapular eruptions within the first day or two after the beginning of penicillin therapy. These are usually mild affairs, lasting but a few days, and do not require interruption of therapy. A slightly larger proportion of patients may have urticaria, which is more likely to occur about a week after the beginning of penicillin treatment but may appear as late as the tenth or twelfth day, and occasional cases of post-therapy urticarias have appeared from two to four weeks after completion of penicillin treatment. Infrequently, these will be severe with angioneurotic manifestations, erythema-nodosum-like eruptions, distressing arthralgias and fever. These more pronounced reactions may require a week or more to subside in spite of all therapy. In most of the urticarias the penicillin may be continued with the assistance of antihistaminic drugs. A still rarer complication is a vesicobullous or pemphigoid type of dermatitis, which can be violent and incapacitating. There is also occasionally observed a localized dermatitis at the site of injections of penicillin. These are ascribed by some to the subcutaneous deposition of the drug, but there is not general agreement on this point. These local reactions respond much better to the application of cold than to hot applications.

In a survey of the treatment of over 10,000 cases of syphilis with penicillin it was stated that no serious reactions were observed.¹³⁶ These authors likened the urticarial reactions to serum sickness. This phenomenon was observed in a few patients as long as two months after treatment had been completed. The incidence of erythematous and papular eruptions in this series was 0.25 per cent. Only 2 patients out of the 10,000 developed a bullous dermatitis, which was limited to the exposed surfaces of the upper extremities. Such a peculiar localization has not been generally characteristic of the bullous type of reaction and suggests the possibility of extraneous or secondary factors. Attention was called to the occurrence of exacerbations of secondary syphilitic lesions, which appeared from the sixth to the tenth day after the start of treatment. This gave the appearance of an actual relapse of secondary syphilis, but darkfield examination of serum from lesions was always negative. No additional treatment was given, and the lesions receded in four or five days. The patients in whom this occurred have had ultimate good therapeutic results from penicillin treatment. Such phenomena seemed to resemble a delayed Herxheimer reaction, although the authors state that the occurrence of a delayed Herxheimer reaction has not heretofore been observed.

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regardless of whether it is topically applied or injected.¹³⁷ Such persons might easily be those who would be more likely to become sensitized to the antibiotic. The fact that severe allergic reactions can occur is stressed in another publication.¹³⁸ In a series of 5000 patients treated with penicillin in an Army hospital, there were 6 reactions of such severity that it became necessary to discontinue the drug. Four were urticarial, occurring early in the course of treatment, 2 were delayed and simulated serum sickness. Preadministration testing for penicillin sensitivity was found to be neither reliable nor practicable.

In a comparison of the incidence of significant penicillin reactions, data were taken from several schemes of therapy as employed on a nationwide basis in many thousand patients.⁷⁰ The rate of reactions per thousand patients was as follows: aqueous solution of penicillin 6.3, penicillin in oil and beeswax 3.1, aqueous solution of penicillin with arsenoxide 15.9, penicillin in oil and beeswax with arsenoxide 7.6. There were 16 deaths among a total of 162,278 patients: 15 in patients treated with aqueous penicillin with arsenoxide, and 1 in a patient treated with penicillin in oil and beeswax with arsenoxide. This is immediate confirmation of the hazard of combined therapy using arsenic as adjuvant therapy to penicillin.

BAL

Although less and less arsenotherapy is being employed, there is considerable literature regarding the value of the relatively new detoxifying agent for metallic therapy known as BAL (2,3-dimercaptopropanol). That BAL has a suppressive action on the treponemicidal effect of the trivalent arsenical preparations has been demonstrated.¹³⁹ Five patients with acute early syphilis were treated with BAL and oxophenarsine hydrochloride concomitantly. The organisms (*Treponema pallidum*) were found by darkfield much longer than they would have been under efficient arsenotherapy. After the termination of the experiment these patients were given sufficient penicillin therapy, and each experienced a Herxheimer reaction equal to or greater than the initial one seen after the first injection of arsenic, which prompted the author to assume that many viable spirochetes were still present at the time penicillin therapy was started.

Unusually good response has been reported with the use of BAL in a series of 44 patients with severe and widespread arsenical dermatitis and that of the acute exfoliative type.¹⁴⁰ Thirty-one of these cases were benefited by treatment, and healing was obtained in an average of twenty-one days. The earliest sign of response was subsidence of the edema. The successful treatment with BAL of severe thrombopenic purpura after antisyphilitic arsenotherapy has been accomplished.¹⁴¹ There was complete recovery among 12 patients between the

of congenital syphilis. This figure dropped to 1.2 per cent in a group of women who had been treated from one to twenty months prior to pregnancy. Even this low figure might have been avoided except for unobserved serologic relapse in 1 uncooperative patient. The recommended dosage is 4,000,000 units of penicillin in twelve days. Patients should be examined at monthly intervals throughout the remainder of the pregnancy with quantitative serologic tests for syphilis to determine evidence of possible relapse and the necessity for retreatment. It is stated that retreatment during subsequent pregnancies is considered unnecessary, provided the patient is carefully observed. In another series of 81 infants born of penicillin-treated mothers with early infectious syphilis, only 1 stillbirth due to syphilis was encountered, and all the remaining infants were normal.¹³² This is a failure rate of 1.24 per cent. A comparable group of infants delivered of women who were treated by various methods of intensive arsenotherapy developed 10.7 per cent of congenital syphilis. That failure rate certainly indicates the superiority of penicillin therapy of the pregnant syphilitic woman. The authors present 2 case reports on mothers who produced infants free of syphilis despite the fact that they themselves showed mucocutaneous relapse after penicillin treatment.

A dose of 3,000,000 units of penicillin for syphilis in pregnancy is advocated from another source.⁷⁶ This amount of the drug was said to protect 95 per cent of the infants when given during the last part of the first trimester of pregnancy. It could be repeated in the third trimester if the mother's syphilis had not responded properly. Still another source recommends 4,000,000 units of aqueous solution of penicillin (every three hours, for 100 doses) with a protection rate of 95 per cent.⁷⁴ It is further stated that in all probability penicillin in beeswax and oil can be substituted for the aqueous solution, in the amount of 600,000 or 450,000 units daily for ten or fourteen days. These studies of the use of penicillin in syphilis of pregnancy tend to confirm earlier optimism.

One previous report of the use of massive arsenotherapy in early syphilis complicated by pregnancy exhibited a degree of success comparable to the best reported with penicillin.¹³³ The reactions to this treatment are excessive, and such hazards are unnecessary in the face of at least equally efficacious penicillin therapy without the dangers of chemotherapy. There seems little excuse for the continued use of arsenic in any pregnant woman with syphilis unless she is unable to tolerate penicillin in any form.

CONGENITAL SYPHILIS

Except in early congenital syphilis, the treatment of this phase of the disease has always been productive of less satisfactory results than most varieties of acquired syphilis. Penicillin has so far brought

about relatively little change in this situation. From the standpoint of the effect of penicillin on the serologic status of congenital syphilis, a series of 25 patients showed improvement in only 24 per cent of the cases.⁹³ Some authors have been most pessimistic about the effect of penicillin in congenital syphilis, one preferring the use of mapharsen and bismuth combined with fever therapy.⁷⁶

Congenital neurosyphilis has been considered one of the most adamant varieties and has not infrequently been recalcitrant to all types of therapy. A group of 11 patients with congenital paresis has been studied for comparison of penicillin with penicillin and malaria.¹¹⁷ Five received penicillin alone, and 6 were treated with the combined method. No significant difference was seen in clinical or spinal-fluid results.

Interstitial keratitis has always provided another complicated therapeutic problem. Klauder¹⁴⁴ reports a study of interstitial keratitis with particular reference to the results of penicillin therapy in a series of 72 patients. It was found that penicillin, like chemotherapy, does not prevent an initial attack of interstitial keratitis, involvement of the second eye, or recurrence of the disease in a previously affected eye. It was possible to evaluate results of treatment of 59 patients in terms of final visual acuity with refraction determined at intervals one to three years after therapy. The findings were compared with a similar group of 54 patients given adequate courses of fever and chemotherapy. There was no appreciable difference in the final visual acuity of the two groups. This lack of striking result in final visual acuity of penicillin-treated patients compared with older methods is consistent with clinical observations in which penicillin does not uniformly exert an immediately favorable effect on active interstitial keratitis. It has long been realized that antisyphilitic treatment is not ideal in the management of interstitial keratitis, but it does show results superior to those in untreated patients. Fever seems to be the most effective single form of therapy but should most certainly be supplemented by adjuvants. Penicillin should dispense with chemotherapy in this situation as in most other phases of syphilis. This opinion is supported by other observers.¹¹⁷

An efficient oral form of antisyphilitic therapy would be of great value for infected infants. There is a report of the use of penicillin dissolved in water and administered to normal uninfected infants at ages of one week to five months.¹³⁴ A dose of 25,000 units gave blood levels that were considered therapeutic for as long as three hours. Further pursuit of this work is surely warranted.

TREATMENT REACTIONS

Penicillin

One of the most remarkable benefits of penicillin has been its relative freedom from reactions, and yet no rose seems to be completely without thorns.

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ages of fifteen and thirty-nine years who had agranulocytosis incurred during arsenotherapy for syphilis and who were treated with BAL.¹⁴² The most dramatic results with the use of this drug have been observed in the sharp reduction of mortality in arsenical encephalitis.¹⁴³ To be effective the drug must be administered within a few hours after the onset of this complication. The dosage of BAL is 2.5 to 4 mg per kilogram of body weight. From four to six injections should be given daily for the first two days, with injections twice a day thereafter until recovery. BAL is considered a specific detoxifying agent for arsenic, mercury, gold and other heavy metals and is given intramuscularly. The antidotal action is considered due to its ability to remove the metal from combination with tissue proteins and the resultant excretion of a stable and relatively nontoxic substance. A review of the subject of postarsenical encephalopathy has recently appeared.¹⁴⁴ Two cases encountered before the days of BAL were described therein, with a description of post-mortem observations. This complication should fortunately be exceedingly rare hereafter with the steadily decreasing use of arsenotherapy.

The successful treatment of trypanosomiasis optic neuritis with BAL has been reported.¹⁴⁵ The usefulness of BAL in poisoning from metals other than arsenic is known. There is recorded another case of successful BAL therapy in gold intoxication.¹⁴⁶

The use of BAL is not unattended by reactions. Patients frequently complain of a tightness in the throat and an oppressive feeling in the retrosternal region. There may be burning of the lips, lacrimation, dryness of the mouth, nervousness and restlessness for periods of several minutes to an hour after treatment. Some patients experience considerable nausea and vomiting. Localized soreness and occasional abscess formation may be observed at the site of injection. The latter is particularly notable in patients with exfoliative dermatitis, as might be expected. Although no severe toxic reactions have thus far been reported, there is experimental evidence of enhanced toxicity of BAL in the presence of hepatic damage.¹⁴⁷ When BAL was injected into animals with severe renal impairment, no evidence of more toxic effects than those in normal animals was obtained.

Other experimental work indicates that thiamine in conjunction with BAL should exert a decidedly complementary effect in the treatment of arsenical toxicity.¹⁴⁸ A severe disturbance in carbohydrate metabolism during intensive arsenical therapy was noted during this experimentation.

SUMMARY

Despite a slight increase in infectious syphilis among the civilian population in the past year, the combined total of early disease among civilians and military personnel has shown a slight down-

ward trend. A ten-year survey of the deaths from syphilis revealed a most encouraging decrease. Control measures are being intensified throughout the country, with emphasis on public education, follow-up study of contacts and recognition of the role to be played by practicing physicians.

Improvement in the repository types of penicillin and wider employment of these products have facilitated the ambulatory treatment of syphilis and greatly reduced its cost to both patients and hospitals. It is surely the most practical approach and maintains adequate therapeutic levels with but one injection in twenty-four hours. For early syphilis, ten daily injections to total 6,000,000 units is the average recommendation, but more may often be advisable. There is continuous investigation of retardants to delay absorption and excretion of penicillin. Adjuvant therapy of assorted types is receiving further attention.

Penicillin G appears to cure about 90 per cent of early cases of syphilis among human beings, but it must be remembered that these patients have been so far followed for but a few years at most. The optimal therapy schedules have not yet been agreed upon, nor is there unanimity about methods of administration. The time-dose relation must be further clarified. Nevertheless, penicillin therapy of syphilis is obviously established by virtue of its shorter time requirement, relative simplicity and strikingly low rate of complications.

Neurosyphilis can apparently be arrested by penicillin in decidedly less time than by any other form of treatment, but adjuvant therapy may have a place in advanced cases. Other types of late or latent syphilis appear to be less favorably affected. All late cases of syphilis, symptomatic or latent, should receive bismuth therapy prior to penicillin to help guard against a therapeutic paradox.

Infection of the fetus will almost invariably be prevented or cured by adequate penicillin treatment of syphilis during pregnancy. Congenital infection is less responsive.

1180 Beacon Street

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ages of fifteen and thirty-nine years who had agranulocytosis incurred during arsenotherapy for syphilis and who were treated with BAL.¹⁴² The most dramatic results with the use of this drug have been observed in the sharp reduction of mortality in arsenical encephalitis.¹⁴³ To be effective the drug must be administered within a few hours after the onset of this complication. The dosage of BAL is 2.5 to 4 mg per kilogram of body weight. From four to six injections should be given daily for the first two days, with injections twice a day thereafter until recovery. BAL is considered a specific detoxifying agent for arsenic, mercury, gold and other heavy metals and is given intramuscularly. The antidotal action is considered due to its ability to remove the metal from combination with tissue proteins and the resultant excretion of a stable and relatively nontoxic substance. A review of the subject of postarsenical encephalopathy has recently appeared.¹⁴⁴ Two cases encountered before the days of BAL were described therein, with a description of post-mortem observations. This complication should fortunately be exceedingly rare hereafter with the steadily decreasing use of arsenotherapy.

The successful treatment of trypanamide optic neuritis with BAL has been reported.¹⁴⁵ The usefulness of BAL in poisoning from metals other than arsenic is known. There is recorded another case of successful BAL therapy in gold intoxication.¹⁴⁶

The use of BAL is not unattended by reactions. Patients frequently complain of a tightness in the throat and an oppressive feeling in the retrosternal region. There may be burning of the lips, lacrimation, dryness of the mouth, nervousness and restlessness for periods of several minutes to an hour after treatment. Some patients experience considerable nausea and vomiting. Localized soreness and occasional abscess formation may be observed at the site of injection. The latter is particularly notable in patients with exfoliative dermatitis, as might be expected. Although no severe toxic reactions have thus far been reported, there is experimental evidence of enhanced toxicity of BAL in the presence of hepatic damage.¹⁴⁷ When BAL was injected into animals with severe renal impairment, no evidence of more toxic effects than those in normal animals was obtained.

Other experimental work indicates that thiamine in conjunction with BAL should exert a decidedly complementary effect in the treatment of arsenical toxicity.¹⁴⁸ A severe disturbance in carbohydrate metabolism during intensive arsenical therapy was noted during this experimentation.

SUMMARY

Despite a slight increase in infectious syphilis among the civilian population in the past year, the combined total of early disease among civilians and military personnel has shown a slight down-

ward trend. A ten-year survey of the deaths from syphilis revealed a most encouraging decrease. Control measures are being intensified throughout the country, with emphasis on public education, follow-up study of contacts and recognition of the role to be played by practicing physicians.

Improvement in the repository types of penicillin and wider employment of these products have facilitated the ambulatory treatment of syphilis and greatly reduced its cost to both patients and hospitals. It is surely the most practical approach and maintains adequate therapeutic levels with but one injection in twenty-four hours. For early syphilis, ten daily injections to total 6,000,000 units is the average recommendation, but more may often be advisable. There is continuous investigation of retardants to delay absorption and excretion of penicillin. Adjuvant therapy of assorted types is receiving further attention.

Penicillin G appears to cure about 90 per cent of early cases of syphilis among human beings, but it must be remembered that these patients have been so far followed for but a few years at most. The optimal therapy schedules have not yet been agreed upon, nor is there unanimity about methods of administration. The time-dose relation must be further clarified. Nevertheless, penicillin therapy of syphilis is obviously established by virtue of its shorter time requirement, relative simplicity and strikingly low rate of complications.

Neurosyphilis can apparently be arrested by penicillin in decidedly less time than by any other form of treatment, but adjuvant therapy may have a place in advanced cases. Other types of late or latent syphilis appear to be less favorably affected. All late cases of syphilis, symptomatic or latent, should receive bismuth therapy prior to penicillin to help guard against a therapeutic paradox.

Infection of the fetus will almost invariably be prevented or cured by adequate penicillin treatment of syphilis during pregnancy. Congenital infection is less responsive.

1180 Beacon Street

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

CASE 35111

PRESENTATION OF CASE

A one-year-old male child was referred to the hospital from a well-baby clinic, where an abdominal mass had been discovered.

The patient was the younger of two living children, and no irregularities were detected regard-



FIGURE 1

ing his birth, feeding or development. Within the two months preceding admission the mother had noticed a firm and painless mass in the child's left flank. He had had constipation, usually relieved by prunes and bran, most of his life, but the mother denied noticing any hematuria.

Physical examination revealed a well developed and well nourished, alert child in no apparent dis-

tress. No lymph nodes were palpable. A prominence of the entire left abdomen was obvious by inspection, and many veins were visible over the abdomen. These were not engorged or tortuous. On palpation the mass was described as being firm, smooth and extending from beneath the left costal margin to the pelvic floor. A small notch was palpable on its medial surface at the level of the umbilicus, the lateral edge was not definitely palpable. There was no evident descent of this mass on inspiration. The liver and right kidney were not palpable. Examination of the chest was essentially negative.

The temperature was 100.2°F, the pulse 110, and the respirations 20-26. The blood pressure was 90 systolic, 50 diastolic.

Laboratory examination revealed a white-cell count of 9300, with 30 per cent neutrophils, 64 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophils. The hemoglobin was 9.9 gm. The red blood cells showed some hypochromia and anisocytosis. The platelets appeared normal. The urine had a pH of 5.0 with a specific gravity of 1.022. The sediment showed 1 or 2 white blood cells per high-power field and amorphous crystals. The nonprotein nitrogen was 30 mg per 100 cc. Nose and throat cultures revealed a few alpha-hemolytic streptococci and *Staphylococcus albus*. A tuberculin test was negative in a dilution of 1:1000. X-ray examinations of the chest, skull and thoracolumbar spine showed no evidence of intrinsic disease. A plain film of the abdomen disclosed a large, oval tumor mass on the left, extending partially across the midline. This could not be separated from the shadow of the left kidney (Fig 1). There was no visible evidence of bone erosion or calcification within the mass. Intravenous dye was excreted slowly on the left, showing marked dilatation and upward displacement of the calyces and pelvis. Excretion on the right appeared within normal limits (Fig 2).

Operation was delayed because of an upper respiratory infection. However, on the tenth hospital day, following transfusion and preoperative doses of penicillin and streptomycin, an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR THOMAS H LANMAN* A painless mass in the left upper abdomen in a one-year-old child brings to mind right off some form of malignant lesion. But before considering cancer in detail we might go through the history, which has some significant points.

The prominence of the abdomen fits in with the tentative diagnosis I have in mind, and the appearance of the veins is interesting but not diagnostic.

The mass is described as firm. I judge it extended into the renal fossa but not into the pelvis. The

*Surgeon, Children's Hospital, Boston.

notch makes one consider the spleen, but as we shall see later it was probably not the spleen. The mass did not descend on inspiration, indicating that it was fairly well fixed. The right kidney was not palpable. The white-cell count showed only a relatively high percentage of lymphocytes, and I do not believe this is significant. There was slight anemia but nothing else abnormal in the blood examination, which is of some significance in excluding certain possibilities such as splenic enlargement.

The finding of streptococci in the nose and throat cultures was probably incidental.

The negative tuberculin test may be significant in some cases but does not enter into this differential diagnosis.

In summary, we have a firm mass that had pushed the intestines over toward the midline. The intravenous pyelogram shows distortion of the kidney pelvis and calyces. Here is a homogeneous mass pushing the bowel over to the opposite side, filling almost the entire abdomen on that side, and possibly extending to the midline but not beyond it. A solid tumor, especially in this age group, should be regarded as malignant until proved otherwise. I do not see anything in the history or in the blood examination to suggest disease of the spleen. The only thing here that might make one think of the spleen is the mention of a notch in the mass. There is nothing to suggest an enlarged spleen caused by either purpura or Banti's syndrome, nor is there anything to suggest hemolytic icterus. One would not expect a spleen of this size at this age without other symptoms of splenic disorder.

What other masses may there be? There are certain benign cysts, and the duplications of the intestinal tract. Cysts of the mesentery are, as a rule, not at all firm. They may attain a size as great as this but would be almost sure, even at this age, to give some gastrointestinal symptoms such as subacute obstruction, vomiting or loss of weight.

A duplication is usually cystic on palpation, but it may feel solid as this did, although it is extraordinarily rare for it to be both large and solid. If attached to the stomach or the bowel and of this size, I believe it certainly would have given something in the way of pressure symptoms and gastrointestinal symptoms.

With a hydronephrosis an enormous mass can occur, but the intravenous pyelogram would not show the abnormality of the pelvis, which we see here. This film shows displacement and compression of the calyces rather than dilatation from a congenital obstructive lesion causing a hydronephrosis in that kidney.

We come now to the types of malignant tumor usual in this age group and in this region. There are two—the embryoma, or Wilms tumor, and the neuroblastoma. In differentiating these two one

can sometimes make a good preoperative guess, although not always. Such a case is a good illustration of when the treatment is surgical, and the mass should be explored.

In addition to the Wilms tumor and neuroblastoma there are rare conditions that one must consider. The true hypernephroma, or Grawitz tumor, we have never encountered in this age. In addition to the Wilms tumor it is possible to have an embryoma arising retroperitoneally from the remains of the primitive mesonephron, which is



FIGURE 2

not attached to the kidney. These are hard to differentiate, but if one attained this size, this picture in the pyelogram, which suggests that the growth is in the kidney itself, would hardly be expected. In considering neuroblastoma, which is by far the commonest of the tumors of neurogenic origin, there are other tumors from the sympathetic system that one might perhaps encounter. Certainly the ganglioneuroma can be quite large, but such size is unusual as early as this.

Adrenal cortical tumors certainly would not attain this size without symptoms, characteristically they are small and, of course, give as outstanding symptoms changes in sex in the male, sex precocity, and in the female, a tendency to masculinization.

The Wilms tumor and neuroblastoma are about even in incidence in our series—93 of the former and 100 or more of the latter. There is not enough difference in numbers to be significant in differential diagnosis. A Wilms tumor usually occurs in early life—most of our cases between two and three

years of age, although we have seen the tumor in patients as young as two months. The neuroblastoma is likely to occur a little later. Three quarters of our cases of neuroblastoma have occurred at four or five years, although we have seen neuroblastoma as early as the seventh day of life. The physical examination perhaps gives a better differential than anything else—that is, the size, the shape and the feel of the mass. The Wilms tumor is smooth or somewhat lobulated, and I would imagine that the notch here was a lobule such as occurs in this type of tumor. A neuroblastoma is more likely to be nodular and rough. It is not always possible to differentiate. It is suggestive that the neuroblastoma usually does not attain such a size as soon as this. Very frequently in cases of neuroblastoma the attention of the mother or the physician may be focused upon the metastasis—that is, there may be evidence of metastasis before the tumor itself is found. Metastases may be seen in the lungs and bones of the skull, but they frequently appear in the long bones. In differentiating these two tumors it is sometimes valuable to take films of the long bones.

The absence of hematuria is not at all unusual. Hematuria is a rare symptom of a Wilms tumor, and certainly not more than a quarter of the patients have had hematuria as a presenting symptom. It is interesting to observe that in such cases the growth had broken through its capsule into the renal pelvis, and as a prognostic sign gross hematuria in a Wilms tumor is a very grave one; we have no case of cure when gross hematuria has been present preoperatively.

In this case from the history, the age and the described feeling of the mass and from the x-ray appearance, I shall make the diagnosis of a Wilms tumor.

DR TRACY B. MALLORY: Dr Wyman, would you like to comment on the films?

DR STANLEY M. WYMAN: I think there are perhaps one or two points to mention. The portions of the mass that one can see extending upward and laterally are extremely smooth in contour. The mass is homogeneous and shows no unusual calcification. The lateral view demonstrates the mass extending downward and extremely far anteriorly up to the abdominal wall. It does not appear to lie very far posteriorly. That is suggestive evidence, not conclusive, but the mass may lie more anteriorly than the kidney. Unfortunately, we do not have pyelogram films taken in an oblique position to determine this. There is a hint of a capsule on this mass, but it is not very definite, and I am not sure it is a valid finding. However, the whole picture raises an additional question in my mind: could this be a cystic lesion, possibly bowel duplication or mesenteric cyst, although it certainly does not sound that way from the physical examination? The large bowel seems to be displaced medial rather than lateral to it.

DR LANMAN: If that is a suggestion of capsule, it would fit in more with a Wilms tumor than with a neuroblastoma.

DR GERTRUD C. REYERSBACH: We wondered clinically about one thing. Was it not a very long interval? It was two months since the mother had discovered the mass, and was not the child apparently well?

DR LANMAN: I do not think that is particularly against a Wilms tumor. These growths go along quite locally and may go for some time. That is one of the most characteristic symptoms we have in our series—that the mother was the first to notice the tumor. The two-month interval here would not be against that diagnosis, though usually the mother seeks advice sooner.

DR J. GORDON SCANNELL: I think that there was universal agreement on the service with the differential diagnosis as given by Dr Lanman. We believed that we were dealing with a malignant tumor and that probably its vascular supply came from above and medially. We therefore elected to explore transthoracically and obtained excellent exposure of the vessels without disturbing the tumor itself. The renal vein was not very large and was divided first. Next the renal artery, as well as a few soft nodes which lay adjacent to it, was secured close to its source. The adrenal gland had previously been clearly visualized, was quite normal and was preserved. The tumor itself was a rather firm, oval mass without great vascularity. It obviously arose in the lower pole of the left kidney. With the vessels previously ligated, the kidney and its tumor were readily delivered and removed. About 15 or 20 cm. of ureter was removed with it.

DR BENJAMIN CASTLEMAN: Would you have given x-ray treatment preoperatively?

DR LANMAN: No.

CLINICAL DIAGNOSIS

Wilms tumor

DR LANMAN'S DIAGNOSIS

Wilms tumor

ANATOMICAL DIAGNOSIS

Cystic teratoma of kidney, benign

PATHOLOGICAL DISCUSSION

DR MALLORY: The tumor was a considerable surprise to all of us since it turned out to be cystic and looked, in fact, almost exactly similar to a multilocular ovarian cyst (Fig. 3). One can see in the lantern slides that the lower two thirds of the kidney have been replaced by a multilocular cystic structure. Some of the cysts have thin and transparent walls, others are opaque. There were a few masses of solid tumor, and those that we found appeared to be fibrotic.

In microscopical sections from this tumor the cysts are lined by a very low, nonspecific-looking, cuboidal epithelium or possibly endothelium. The interstitial tissue consists almost entirely of fibrous tissue, most of which is well differentiated, although some is cellular in places and here and there, scattered through the tumor, are multiple, well differentiated, striated muscle fibers. These convince me that this was a teratoma that had differentiated in only two or three directions. We found nothing suggestive of teeth, hair, squamous epithelium and so forth, such as we sometimes find in teratomas. Teratoid tumors, of course, are found in the kidney and in the region of the kidney. Sometimes it is difficult to decide where they actually

per cent survival, from 1931-1939, 30 cases with 10 cures, a 33 per cent survival rate, from 1940-1947, 37 cases with 19 cures, a survival rate of 49 per cent. We regard a two-year postoperative interval with no symptoms of recurrence as a cure in this condition. But the most interesting feature in this study is that of these 93 cases, 63 per cent of the cures have been in patients one year old or younger, and in the last studied group, 1940-1947, 80 per cent of the cured patients among the 37 cases were younger than one year. In other words, it is in the early age group that prognosis appears to be best. Here is a condition that certainly justifies routine examination in the early months or years of life because these tumors frequently give no symptoms whatever until the mass is noted by the mother or by a physician. This present case is an extremely interesting type of tumor. I have never seen one like it.



FIGURE 3

arise. In this case there is no question that the tumor was intrarenal and was occupying the entire lower pole. I have never seen a tumor of this character, although I do not know whether in the material at the Children's Hospital you have.

DR LANMAN: No, we have not. What do you think about its degree of malignancy?

DR MALLORY: I think it was probably benign. We could find no foci typical enough to suggest malignancy. I would offer a good prognosis in this case.

DR LANMAN: I think it is an interesting case, and it is certainly new to me as a type of tumor in this region. The history is characteristic of embryoma. I think the treatment is the same in any case, and it brings out that exploration is the only way to decide what the tumors are. We are very much against the punch-biopsy type of diagnosis and are against preoperative radiation. I recently looked up our series of 93 cases of Wilms tumor from 1914-1947 and was encouraged to find that we have an over-all cure rate of 35 per cent. From 1914-1930 there were 26 cases with 4 cures, a 15

CASE 35112

PRESENTATION OF CASE

First admission. A twenty-six-year-old woman was admitted to the hospital because of hemoptysis.

Six years before admission the patient was suddenly seized with pain in the left lower chest. This was accompanied by fever and malaise. The fever and pain disappeared in the course of ten days. Two weeks later she developed a dry, hacking cough, which soon became productive. She did not return to work as a playground instructress for three months and shortly after this began coughing blood, about 7 cc daily, for four or five days. She had lost 20 pounds since the onset of the illness. The next three years were spent in bed, during which time a diagnosis of bronchiectasis of the left lower lobe was made. Treatment by weekly bronchoscopies and postural drainage cleared all the symptoms. She was perfectly well until six months before admission, when she had a repetition of the first illness. In spite of postural drainage and therapeutic bronchoscopies the bleeding continued.

Physical examination revealed dullness and flatness over the left base, decreased breath sounds and a few, fine rales. A chest x-ray was reported as follows:

There is a rounded, sharply defined, dense shadow lying in the costovertebral angle on the left side just above the diaphragm. This shadow measures about 2 cm in diameter and has very smooth, sharp borders. There is also generalized haziness in the lung field medial to the shadow. This shadow has the appearance of a foreign body. After injection of lipiodol there are numerous, dilated, clubbed bronchi in the lower lobe. The shadow previously described has the same density as lipiodol, probably representing a puddle of lipiodol from a previous injection.

A left phrenicectomy and left lower lobectomy were done. Except for phlebitis the convalescence was uneventful. On x-ray examination two months

later the stump of the main bronchus of the lower lobe appeared slightly widened and had some minor bronchi branching off in this region. These bronchi were surrounded by a soft-tissue mass, measuring about 5 cm in diameter, which may have represented the residue of the lower lobe.

Second admission (fourteen years later) Following discharge the symptoms all cleared except for hemoptysis, which occurred at intervals of six to

leaf of the diaphragm was elevated. There was thick pleura in the left base, this was probably the result of the previous operation. The left upper lobe and the right lung were clear. There was a slight shift of the mediastinum to the left (Fig 1 and 2).

On the second hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR JOHN W STRIEDER* Whatever the cause of bleeding, which began some twenty years before entry, it was obviously not relieved by the left lower lobectomy, which was performed fourteen years before entry. It may therefore be assumed that the cause was not in that portion of the lobe removed at the time of lobectomy. I say "portion" advisedly because in that era tourniquet lobectomy



FIGURE 1

twelve months. The episodes were not associated with coughing. Six months before admission the patient noted increased frequency of hemoptysis and a sense of tightness beneath the lower sternum. This was associated with the taking on of extra household responsibilities. Usually the amount of blood varied between 30 and 90 cc. The episodes occurred mostly at night and every two or three weeks. There were no other symptoms.

The temperature was 99.2°F, and the pulse, respirations and blood pressure were normal.

There were dullness, decreased tactile fremitus, decreased bronchovesicular breath sounds and decreased spoken and whispered voice over the left posterior lung base. The hemoglobin was 12 gm, the white-cell count was 7900, with a normal differential. The urine was normal. An x-ray of the chest was reported as showing a rounded area of increased density, 5.5 cm in diameter, in the posterior portion of the left chest at the site of the previously resected left lower lobe. The upper margin of this soft-tissue shadow was adjacent to the intermediary bronchus on the left. The left



FIGURE 2

was the universal technic whereby pulmonary tissue was removed. For those who are not derived of that era, let me say that tourniquet lobectomy removed varying amounts of the lobe and left stumps of varying size, containing varying lengths of residual bronchi depending upon the site of amputation of the lobe. The pedicle was treated with hemostatic ligatures of catgut and, usually, pleuralized. In treating patients by modern operative technics a number of years after lower lobectomies by the tourniquet method, I have been impressed by the amount of pulmonary tissue that had been left

*Surgeon-in-chief for thoracic surgery Boston City Hospital

It has frequently been a source of wonder to me that the operation was so often successful to the degree that it was

At this point the exercise, therefore, resolves itself into a discussion on the basis of deduction to determine the source of bleeding. Was it in the left lower lobe, or was it in some other portion of the bronchopulmonary system? I think it is reasonable to assume on the basis of the record, there being no evidence to the contrary, that this patient's bleeding did come from the left lower lobe. So that it remains to determine what the nature of this lesion was that persisted in troubling this woman by repeated hemoptyses over a period of twenty years.

May we see the x-ray films?

DR STANLEY M. WYMAN: These films of the chest show the left leaf of the diaphragm to be elevated, with thickening of the superior border as a result of the old operation. The heart and mediastinum are displaced slightly toward the left. The overexposed grid film demonstrates a somewhat lobulated, homogeneous, sharply defined shadow in this region, which lies just about at the end of the stump of the left-lower-lobe bronchus. The shadow is seen in the lateral view to lie posteriorly, also in apposition with this major bronchus.

DR STRIEDER: Would you have any opinion about its density? Is it a solid tumor? Is it consistent with a cyst filled with fluid?

DR WYMAN: Unless the cyst contains fairly fatty material, I believe it would be the same density as a soft-tissue tumor. The suggestion of perhaps a little lobulation makes one wonder about the actual soft-tissue mass. There is a little irregularity of the contour. This is insufficient to allow me to say whether this is definitely a soft-tissue mass or a cyst, although I would lean toward the former.

DR STRIEDER: Are there flecks of calcium in it, or are these densities due to overlay?

DR WYMAN: I think it is overlying the shadow. The lung fields otherwise appear clear.

DR STRIEDER: So we have evidence of a round density, which, by comparison with the description of the films taken fourteen years previously, two months after operation, is similar in size, contour and density. The original films are not available, of course. The nature of the shadow described in the original films as being possibly a foreign body and then described as of the same density as the

lipiodol (and therefore suspected of being a residuum of a previous lipiodol injection) is a matter of conjecture. I think one cannot say more than that about it. That shadow was not present after the operation, so that whatever it was, it was apparently removed at the time of lobectomy.

Given an x-ray shadow that is suggestive of tumor within the thorax, any discussion as to the exact histopathology of the tumor resolves itself into a more or less philosophical exercise that, at best, is a poor substitute for the microscope once the specimen has been handed to the pathologist by the surgeon. The cogent question at the present is, What lesion that is familiar to me best satisfies the many facets of this history and would give all the end results described? To me, by all odds, the so-called bronchial adenoma best satisfies this history. Going back over the history, the onset suggests bronchial obstruction followed by atelectasis, with infection and the subsequent development of bronchiectasis. The patient had intermittent bleeding for twenty years in varying amounts. These occurred during the third and fourth decades in a woman who, at the onset, was nineteen or twenty and who, at the time of the last admission, was about forty. This also is consistent with so-called bronchial adenoma. She had a long course of bronchoscopies, and certainly during the course of these bronchoscopies it might well have been suggested that she had an obstructive lesion in the nature of an adenoma causing her difficulty. However, we have no information on that, and of course it is entirely possible that the tumor was beyond the range of vision of the bronchoscopist. But full cognizance was not taken of the obstruction or the compression that it might have caused. She came to operation, and a tourniquet lobectomy was performed. A small tumor, suitably located extrabronchially in relation to the intermediary bronchus, could have escaped inclusion in the amputated specimen. That is a possibility that we have to consider. We do not know what the specimen showed at the time of the original removal. If the lesion escaped, as I think we can assume it did, that is a satisfactory reason for her continuing to spit blood up to the time of her last admission. If it was an adenoma, the question comes up whether or not it had undergone malignant degeneration as these tumors are alleged to do by many competent observers. We have no

evidence from which I can deduce that it had undergone malignant degeneration, but I would say that the periodic hemoptoic episodes were against cancer. The malignant tumor that ulcerates tends to bleed day after day for periods in small amounts rather than to cause small, frank hemoptyses, which are consistent with adenoma.

Of course, other causes of bleeding should be considered. Tuberculosis is not suggested in any way by the films, the course or the laboratory data with which we are furnished. Other tumors that cause bleeding most commonly are the malignant tumors. Benign tumors, other than the so-called benign adenoma, are likely to cause bleeding on the basis of obstruction and infection. Again, we have no way of knowing whether she had obstruction with bronchiectasis and bleeding from it alone.

One other hypothetical possibility that appeals to me — it is hypothetical because I have not encountered it personally, nor have I seen it described in exactly this situation — is that the original episode was on the basis of infection and atelectasis and that she developed bronchiectasis without an obstructing lesion in the bronchus. In that case, she bled on the basis of bronchiectasis, and when the lobe was amputated by tourniquet lobectomy radicles were left from which she continued to bleed. To go farther, she may well have developed a bronchiectatic cyst by the same mechanism that we have seen bronchiectatic cysts develop in residual lobes unrecognized as having disease in them prior to the time of operation. Against this is the fact that she is not described as having sputum. We would expect her to have sputum unless there was complete isolation of the cyst from the main bronchial tree. There were no febrile episodes. I would think somewhere along the line she would have had a bout or two of fever, if a reservoir had developed. Finally, as described by the radiologist, the tumor appears solid rather than cystic, but this of course is relative. So although this possibility is attractive, I would discard it in favor of my first impression, and say that this patient had bronchial adenoma with the question of malignant degeneration.

CLINICAL DIAGNOSIS

Bronchial adenoma

DR STRIEDER'S DIAGNOSIS

Bronchial adenoma

ANATOMICAL DIAGNOSIS

Bronchial adenoma

PATHOLOGICAL DISCUSSION

DR TRACY B. MALLORY: At this point the aid of the bronchoscopist was sought. Will you tell us your findings, Dr. Benedict?

DR EDWARD B. BENEDICT: Bronchoscopy showed a small, round tumor about 1 cm. in diameter below the left-upper-lobe orifice, which bled rather easily. It was far enough below the orifice that I thought



FIGURE 3

simple resection of the stump of the bronchus could be performed.

DR J. GORDON SCANNELL: This patient was operated on by Dr. Edward D. Churchill on both occasions — in 1935 and again recently. As Dr. Strieder pointed out, a tourniquet lobectomy was done fourteen years previously. It is well recognized that a surprising amount of lower lobe may be left behind on such occasions. Apparently, there was no evidence at that time of an adenoma, and the procedure went uneventfully. At the second operation a tumor was obvious, lying in the region of the resected lobe, and this remnant was 4 or 5 cm.

in its three dimensions. It lay under the upper lobe, very much like a ball in a catcher's glove, and although endoscopically it might have been resected without sacrificing the upper lobe, surgically the blood vessels, arteries and veins to the upper lobe made it impossible to resect and preserve that lobe, and a pneumonectomy was therefore completed. That was done for technical reasons and not with the idea that this was a malignant tumor. There were no suspicious lymph nodes seen at operation.

DR MALLORY: I have a picture of the resected specimen (Fig 3). This is the upper lobe. I do not think that one can quite see the intrabronchial tumor. It was comparatively small, about 0.5 cm in diameter. External to that was this quite large mass, varying from 3 to 4 cm in diameter, lobular, quite firm and apparently well encapsulated. There were a number of regional lymph nodes, none of which appeared to show any involvement. Histologically this was a very characteristic bronchial adenoma of the type that closely resembles the carcinoids of the intestinal tract. The tumor consists of small bundles of epithelial cells anastomosing very widely with one another. The cells are uniform in size and character and occasionally in places in the tumor there is a suggestion of gland formation, but these are not true glands. They represent areas where the stroma has degenerated, leaving an apparently cyst-like space. These tumors are not infrequently invasive and do occasionally show metastases to regional lymph nodes and rarely show

distant metastases. In this case, in spite of twenty years' duration, it had not reached the lymph nodes.

DR ALFRED KRAVES: Did the original specimen show anything more than bronchiectasis?

DR MALLORY: That is all. The amputation had been below the level of the main bronchus. These tumors are often dumb-bell in shape, with a small nodule within the lumen of the bronchus and another nodule outside the wall. The external tumor is sometimes very much larger than the internal tumor, as it was in this case.

DR STRIEDER: I have not heard you state recently your impressions of the possibility of malignant degeneration of these tumors.

DR MALLORY: I have not seen any histologic evidence of a shift of the degree of malignancy. I think they are potentially of very low malignancy, and the ones that do invade and reach the regional lymph nodes do not look under the microscope any more malignant than the others. I think the situation is exactly analogous to the carcinoids of the intestinal tract, which can also be locally malignant and rarely produce distant metastases.

DR STRIEDER: You believe, then, that bronchiogenic carcinoma is never on the basis of such a precursor?

DR MALLORY: I do not believe there is any connection between them.

DR BENJAMIN CASTLEMAN: I believe we have had 40 or 50 cases of adenoma of the bronchus, and in only 1 was there a metastasis to a regional lymph node.

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MEDICAL MANPOWER

IN THESE feverish days of reports, programs and proposals, a report has just appeared that is of vital interest to every thoughtful citizen and particularly to the physician, because its central theme is medical manpower. It is the so-called Voorhees report, the unanimous report to the Hoover Commission of the 11 medical and 5 lay members of the Committee on Federal Medical Services. This eighty-nine page document, supported by twelve detailed appendixes, is factual, unbiased and affirmative. It describes the magnitude of federal medical commitments, reveals administrative weaknesses and proposes drastic remedies. It is timely, because this country has reached the point where its bankruptcy in either money or manpower can

cost mankind that freedom for which it is desperately fighting throughout the world.

The United States gives varying degrees of (medical) care to 24,000,000 beneficiaries — about one-sixth of the nation. Four big and some forty smaller agencies of the government spent about one and one quarter billion dollars for health and medical services in fiscal year 1948, an increase of five times over 1940, and of 20 per cent even over 1947. In 1949, the V. A. alone will spend as much as all forty-six agencies did in 1948 — half of it for new hospitals. This enormous and expanding enterprise is devoid of any central plan.

The Government is competing against itself. Not only are federal hospitals being built alongside existing unused federal hospitals, but also they are being built in places where they cannot be staffed. "Nearly half of the 89 new V. A. hospitals are being built or planned in areas where experience has proven that it will be difficult, if not impossible, to secure adequate staffs." Construction is far out-running medical manpower. "In the V. A. alone, 5,600 beds are now closed because of inability to staff them." The armed-forces expansion program, on which peace is believed largely to depend, faces shipwreck on the rock of medical-manpower shortage, both quantitative and qualitative. In the race for manpower to serve a sixth of the nation the federal agencies are competing not only against one another but also against the five sixths now receiving federal aid under the recent Hill-Burton Act.

Unpalatable remedies are courageously and unanimously proposed by the Voorhees Committee. Waste must be eliminated, existing manpower must be efficiently used. Only by a unified system of federal hospitals can high-quality care in peace and national protection in war be achieved. Many federal hospitals, including Veterans Administration, Public Health Service and certain military general and even station hospitals at home, will be regrouped under a new nonmilitary Cabinet Department.

Our area surveys, which covered about one-sixth of the country's Federal hospital beds, showed that new construction costing over \$100,000,000 could probably be saved in these areas alone by such a plan. Except in war, if adequate care is to be given, specialists must be utilized in their home communities.

The armed forces, merged or unmerged, will retain military hospitals overseas and certain large

medical centers and certain small installations at home posts in remote districts, but unnecessary duplication will be avoided and supervision will be exercised by a deputy of the Secretary of Defense aided by an advisory committee including civilian doctors

There will be a unified medical supply system for all federal depots. Efforts to control and eliminate disease will be intensified. Medical research and training will cut across boundaries of service, department and government. The report ends

We have attempted to outline a method which we hope will correct the extravagance resulting from the present series of unrelated projects, and weld these together into an integrated, orderly whole. With such an organization, staffed with outstanding personnel, it should be possible to utilize our unequalled medical resources to the maximum, and by intelligent planning take steps which will make us a healthier and stronger nation

If these proposals sound Utopian it means that they are being viewed from a parochial or traditional position that no longer exists in hard reality. They must be considered in the light of a world situation, critical now, and bidding fair to remain so for years. No resting place has been reached on the climb toward security and freedom. The sacrifices ahead may be greater than those behind. Apathy is to be expected. Opposition is to be expected, both sincere and cynical. Understandably, life-long traditions and habits of thought will be hard to change, and all honest doubts arising from this quarter will merit sympathy and respect. Regarding opposition motivated by conscious self-seeking, no comment need be wasted. All but two of the first forty nation-wide editorials acclaimed the Voorhees report with enthusiasm, two were critical or neutral. Admittedly, this is only a beginning, but it appears to point the right direction. Those who presently face perplexing problems of medical and financial readjustment will want to read this report and draw their own conclusions

CATARACT IN CYCLOTRON WORKERS

THE recognition of cataracts apparently related to exposure to irradiation in 5 of the pioneer physicists working with cyclotrons brings a sad reminiscence of the early workers with x-rays and radium

However, there is a point of contrast. Cataract is a condition that can usually be operated upon and corrected successfully. The skin changes and the changes in the hematopoietic tissue of the early x-ray workers could not be corrected.

At the present time studies have not progressed to the point where any common factor in these cases, other than exposure to radiation from the cyclotrons, has been determined. However, there is some evidence that exposure of the eyes to neutrons if the worker looks into the beam of the cyclotron or directly into the target area is an important factor. This practice, once possible, has been eliminated by adequate safeguards.

It has been clearly established by experiments carried on under both the Manhattan Engineering District and the Atomic Energy Commission that, on the basis of the present methods of physical measurement, the biologic effectiveness of a given dose of neutrons as measured by physical means is greater than that of roentgen rays or gamma rays by a factor of 8 or 10 at least. This greater effectiveness hinges on the nature of the neutron, which carries no external electric charge, penetrates tissue readily and may hit several atoms, producing ionization at each hit.

One of the unfortunate aspects of the development of these cataracts is that they apparently were in a sense needless — that is, some persons at least departed from the known safety standards for operation and took what might be called a calculated risk (exceeding the known permissible dose of 0.1 r per day) deliberately to expedite the scientific work on which they were engaged. One of the continuing problems of all physicians and biophysicists having to do with safety monitoring is to counteract the natural enthusiasm of the scientist, which leads him to attempt shortcuts that appear reasonable from the standpoint of his science but are unsafe from the standpoint of biologic experience. In a sense, in establishing standards of permissible dose some recognition of this has been made since the standards under which the Atomic Energy Commission and its contractors operate, for example, are set with a very appreciable factor of safety. The standards permit continuing exposure over twenty or thirty years' time, with

safety Research is being initiated to determine the sensitivity of the lens to neutrons. It has already been established as the most sensitive structure in the eye to roentgen rays.

It is perhaps worth noting that in the making and handling of about $2\frac{1}{2}$ pounds of radium up to 1941, the total amount then isolated in the world, about 100 deaths may be ascribed to radium, only 2 deaths may be ascribed to the handling of material equivalent to hundreds of tons of radium under the Manhattan Project and the Atomic Energy Commission.

THE NATURAL HISTORY OF DISEASE

MAN is subject to a great variety of diseases and it has always been one of the main functions of clinical research to provide accurate descriptions of these various pathologic entities. The characteristics of most acute diseases and of the acute phases of most chronic diseases have been reasonably well defined. With some notable exceptions, however, accurate descriptions of the entire courses of common, chronic conditions are woefully lacking.

Essential hypertension is a case in point. It is known that some patients with this disease rapidly develop incapacitating symptoms and that others go for many years without inconvenience of any sort. It is also known that some patients develop a type of hypertension that proceeds with such extreme rapidity and is associated with such extensive vascular damage that the process is quite properly designated malignant. The outlook for the patient with this form of the disease is undeniably bad, but what of the prognosis in a case of ordinary benign essential hypertension? Some investigators regard any type of hypertension as a highly dangerous disease, and believe that the prognosis is relatively poor. The practicing physician is more apt to view mild or even moderate elevations in blood pressure with less alarm, knowing that many patients with hypertension remain asymptomatic for decades. Neither view regarding the outlook in benign essential hypertension can be proved right or wrong, since most clinical descriptions of the disease cover too short a period in its course or are based on more or less selected case material. That more adequate

studies are needed is very clear indeed, particularly to anyone who wishes to compare a group of treated with a group of untreated cases. The advocates of sympathectomy for the treatment of benign essential hypertension have amassed an impressive amount of data on the effects of the operation up to ten years after surgery. Unfortunately, it is still not possible to prove unequivocally that this or any other type of treatment significantly lengthen the life of the patient with benign essential hypertension. What is lacking is a long-range study of a large number of unselected and untreated cases of the disease to serve as a base line. The recent studies by Burgess¹ and by Bechgaard² are steps in the right direction, but many questions still remain unanswered.

Another prominent example is duodenal ulcer, the natural history of which remains shrouded in uncertainty and in which, as in essential hypertension, the value of the several forms of therapy cannot be determined until the course of the untreated disease is accurately mapped. Still another example is glomerulonephritis, although many of the more pressing questions regarding the disease have recently been answered by Addis³ by means of a long-range study. Cardiovascular degenerative disease is at last the focal point of an integrated attack by a group of investigators whose plans call for a ten-year period of study.⁴

It is understandable, in view of the numerous difficulties involved, that relatively few investigators have undertaken long-range studies of disease. Certainly, the general methods used by Addis and by Bechgaard are to be emulated when possible but there are other approaches to these problems. There is, for example, a vast store of information locked up in the record rooms of hospitals and outpatient departments that could and should be ferreted out. A record survey, particularly if combined with a determined attempt to follow up patients whether dead or alive, may prove to be an extremely valuable contribution. Although the results of such a study may not be entirely applicable to a community as a whole, they at least provide information covering the hospital or outpatient department population. Record research of this type is often looked upon as the stepchild of medical

investigative endeavor, but if pursued critically it always yields information of value. Furthermore, unless such use is made of hospital records, the careful recording and filing of clinical data loses much of its value and becomes increasingly hard to justify.

Data obtained by the military services can provide a starting point for inquiry into the natural history of certain diseases in young men. Several major research projects, utilizing such data have been initiated by the Veterans Administration. Furthermore, life-insurance statistics, although often based on highly selected samples, cannot be dismissed as valueless if the findings are not too broadly applied.

The time has surely come when the large gaps in the knowledge of long-term diseases should be closed. Not only should more long-range study projects be set up but also the data already at hand should be arranged and organized so as to obtain all possible information from it. It is decidedly paradoxical that so much investigative effort should have been spent on therapy when so little is known about the diseases against which the therapy is directed. The present trend toward long-range studies should remove the paradox and may go far toward enabling investigators to devise more rational and effective therapeutic methods.

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FELLOWSHIP FOR FREEDOM

A "FELLOWSHIP for Freedom in Medicine," according to the *British Medical Journal*,* was formed by 700 British physicians at Caxton Hall, Westminster, on Saturday afternoon, November 13, 1948, Lord Horder being "unanimously acclaimed to the chair." The meeting was the eventual response to a letter from Lord Horder printed in the *British Medical Journal* in June, some 1750 letters had already been received as a result of this communication.

*National Health Service. Fellowship for freedom in medicine. Supplement to the *British Medical Journal* 2:180, 1948.

tion, and they were still arriving at the rate of 15 to 20 a day.

Among the reasons for the surrender of British medicine in the summer, Lord Horder averred, were "a secretariat swollen in numbers and influence, much going and coming between it and Whitehall, too strong a tail wagging too weak a dog, machinations, thought by many to be both meddlesome and mischievous, on the part of men holding key positions outside the [British Medical] Association" — (applause) — "and, if I may plagiarize Milton, 'blind mouths' at the centre and at the periphery, 'hungry sheep' looking up but not being fed."

Part of the cause of the collapse, Lord Horder stated, was lack of an appreciation by the medical profession of its value in society. Its members let themselves be used "as pawns in the game instead of being master pieces."

"We are no longer experts," the chairman continued. "We sit and sign forms. With no time to diagnose their diseases, we pass our patients to other persons and to institutions, knowing full well that these cannot dispense the health benefits which may or may not be needed."

The sense of the meeting was that the standard of medical practice had fallen and was likely to fall still further, that the Fellowship for Freedom in Medicine should be in the nature of a guild to nurture the ideals of the profession until it might again be free.

British medicine may have become enslaved by politics, but it is apparently struggling inside its chains. Let American medicine look to itself that it may preserve its own freedom.

EASTER SEAL CAMPAIGN

THE Bay State Society for the Crippled and Handicapped, Inc., opens its fourth annual Easter Seal campaign today. The purpose of the drive is to raise \$275,000 — an increase of approximately \$73,000 over last year's receipts — for the support of six major treatment centers in the Commonwealth, as well as a program of medical care and employment for disabled persons, summer-camp vacations for handicapped children and prosthetic

devices for cripples. The projects operated or partially supported by this organization include a nursery school in Boston for children with cerebral palsy, a seizure unit at the Children's Hospital for the diagnosis and treatment of epilepsy, a curative workshop for the rehabilitation of the orthopedically handicapped and treatment and training centers for patients with cerebral palsy.

There is no denying the value—to the patient and the community alike—of rehabilitation and training of disabled persons. The campaign, whose success will ensure continued functioning of these vitally necessary activities, deserves the active support of physicians and laymen alike.

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OCCUPATIONAL MEDICAL CLINIC AT MASSACHUSETTS GENERAL HOSPITAL

To the Editor From 1911 to 1928 the Massachusetts General Hospital conducted what was known as the Industrial Clinic for the study and care of workers thought to be disabled because of occupational hazard.

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An organization of the Alumni of Children's Hospital, Washington, D. C., is being undertaken. The Children's Hospital Alumni Charter Meeting will be held on April 5 in Washington, D. C.

Further information may be obtained from Dr. Alfred T. DeVito, chairman of the Organization Committee, Alumni Association, Children's Hospital, Washington, D. C.

THE FOUNDATION PRIZE

An award entitled "The Foundation Prize" has been established by the South Atlantic Association of Obstetricians and Gynecologists. Authors of papers on obstetric or gynecologic subjects desiring to compete for the prize may obtain information from Dr. E. D. Colvin, secretary-treasurer, South Atlantic Association of Obstetricians and Gynecologists, 1259 Clifton Road, N. E., Atlanta, Georgia.

(Notices concluded on page 4111)

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VIRAL HEPATITIS*

A Consideration of Certain Aspects of Current Importance to the Practicing Physician

JOHN R. NEEFE, M.D.†

PHILADELPHIA

DURING recent years, the importance of viral hepatitis as a public-health and military problem has become increasingly apparent. The term "viral hepatitis" is used to include as a group the forms of hepatitis caused by filterable infectious agents that apparently are primarily hepatotropic and produce, as their outstanding clinical manifestations, evidences of liver injury that may or may not be associated with phenomena suggesting an infectious origin.

Viral hepatitis thus includes the two types of disease commonly referred to as infectious (epidemic) and homologous serum hepatitis. The available evidence indicates that at least two filterable agents, which tentatively can be classified as viruses, are concerned¹⁻⁵. One, referred to below as virus IH, has been identified primarily with the clinical and epidemiologic syndrome of infectious (epidemic) hepatitis, which usually has an incubation period of fifteen to forty days. It perhaps has not been generally recognized that this virus may also be responsible for so-called "homologous serum hepatitis" occurring fifteen to forty days after "parenteral exposure" to a source of the virus through one of the mechanisms discussed below. More familiar is the classic syndrome of homologous serum hepatitis, the most distinctive feature of which is the long interval of two to four and a half months that elapses between "parenteral exposure" and the onset of the overt disease. The other of the two viruses mentioned above, and subsequently referred to as virus SH, appears to be mainly responsible for this syndrome. Homologous serum hepatitis thus should not be regarded as a single etiologic entity.

Evidence for the existence of at least these two hepatitis viruses (IH and SH types) has been

described in detail elsewhere¹⁻⁵. Further discussion here does not seem warranted except to call attention to the fact that the differences that have been demonstrated between these two types of hepatitis virus stand strongly on the mutually confirmatory experimental results obtained by three independent groups of investigators¹⁻⁵ and are supported by a large body of epidemiologic evidence^{1, 6, 7}. Efforts to account for the various syndromes of viral hepatitis on the basis of a single virus fail to explain the consistent short incubation period following parenteral injection of IH viruses, the failure of SH viruses to induce overt disease when administered orally, and the lack of resistance (cross immunity) to infection by one virus in the presence of resistance (homologous immunity) to reinfection by the other.

At the present time, however, the problems presented by the two recognized types of viral hepatitis overlap, and, as no clinically applicable method for their specific differentiation has been developed, it is practical and useful to consider them together under the group term "viral hepatitis."

PUBLIC-HEALTH ASPECTS

Considered in the above sense, viral hepatitis is a widespread disease of high sporadic and epidemic incidence. The actual incidence must be considerably higher than the apparent incidence since the disease unfortunately is not universally reportable and because many cases, particularly those in which jaundice does not become overt, are unrecognized. The recognized cases alone, however, are sufficiently frequent to warrant recognition of viral hepatitis as an existing and potential public-health problem of major importance.

SPECIAL PROBLEMS IN DIAGNOSIS AND MANAGEMENT

Of considerable interest and clinical significance is the fact that viral hepatitis is being recognized with increasing frequency as an important cause of jaundice in the older age groups. Most of the infections in these patients appear to be of the virus

*This paper and the following two papers were presented as a symposium on liver diseases at the annual meeting of the Massachusetts Medical Society, Boston, May 26, 1948.

From the Nutritional Service of the Department of Pediatrics and of the Gastrointestinal Section of the Medical Clinic, Medical School and Hospital of the University of Pennsylvania.

†Associate in medicine, Medical School and Hospital of the University of Pennsylvania, and National Research Council Senior Fellow in the Medical Sciences.

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(Notices concluded on page xiii)

No extrahuman host has as yet been recognized. Therefore, discussion must at present start and end with the human host (Fig 1). Hepatitis viruses IH and SH may both be acquired from human blood. Only the former has been shown to be present in the feces. Neither has been proved conclusively to be present, or absent, in urine and nasopharyngeal secretions, but present information suggests that these are not potent sources of hepatitis virus, at least during the active stages of the disease. Transmission of hepatitis virus IH from feces through one or more of the mechanisms shown in Figure 1 probably accounts

signs, it is not known whether the virus persists or recurs in the blood after recovery from acute hepatitis, development of a method for inactivating the virus in whole blood or plasma will solve only part of the problem, the virus in human serum albumin solutions is apparently inactivated by present methods of processing (heating at 60°C for ten hours). In Figure 1, the recognized mechanisms through which the hepatitis virus may be acquired from blood are enclosed in solid lines. Three of these — namely, the use of human blood, plasma or serum for transfusion, passive immunization and as a component of biologicals — are well established

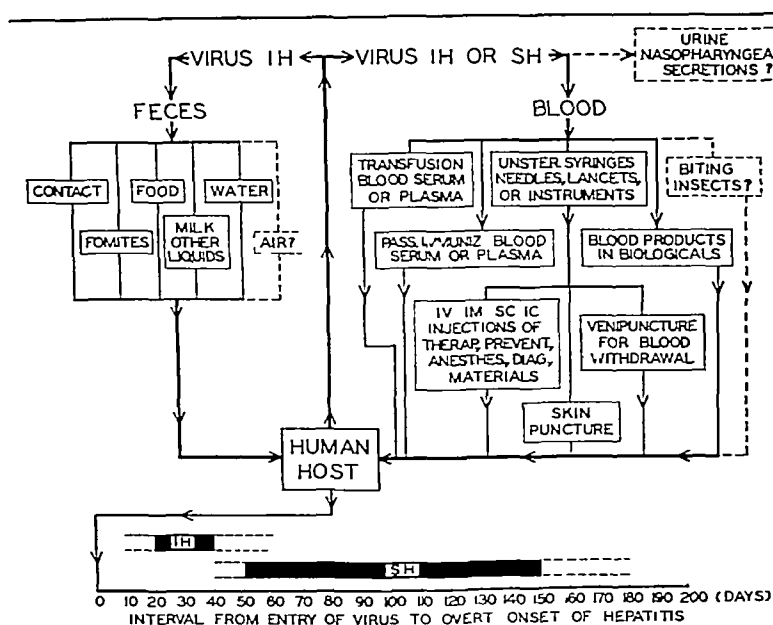


FIGURE 1 Concept of the Etiology and Epidemiology of Viral Hepatitis

for a large proportion of the naturally acquired infections, both sporadic and epidemic. At the present time, there is little that one can do to interrupt this chain of events other than apply the usual sanitary measures indicated for control of all intestinal pathogens.

The mechanisms of transfer of hepatitis virus through blood and its derivatives are of particular interest. The special factors involved in the prevention of blood transmission include the fact that minute quantities (0.01 cc or less) are infective, all methods developed to date that are capable of inactivating the virus in blood or plasma render these materials unsatisfactory or unsafe for human use, there is as yet no practical method for detecting the virus in blood or plasma, and no method for detecting infected donors, as pointed out above, the viruses may appear in the blood without previous, associated or subsequent symptoms or

links in the epidemiologic chain.¹ Transmission through these mechanisms is not yet completely preventable, but the frequency can be decreased by recognition and adherence, so far as possible, to the following principles: transfusion of the blood, plasma or serum should be avoided whenever possible and used only when the indication is greater than the risk (the choices in order of increasing risk are human serum albumin, whole blood, single plasma units, cross-matching beings required, small plasma pools and large plasma pools), donors should be excluded if they have been exposed to a potential source of the virus during the preceding six months, if they have had unexplained or positive symptoms during the previous six months or if icterus, hepatomegaly and positive laboratory findings are present at the time of bleeding, the recipient's record should contain data identifying the product received, and the blood-bank record should

SH type, and the increased incidence probably results in part from the greater frequency with which older persons are being exposed to the mechanisms whereby blood transmission of virus may occur. Possible explanations for the apparent predominance of virus SH types of infection in the older age groups have been discussed elsewhere.¹ Suffice it to say here that viral hepatitis not only is the most frequent cause of jaundice in children and young adults but also must now be regarded as a frequent cause of jaundice in older persons. This is of considerable clinical significance because the onset, particularly of the SH type, frequently is relatively silent and the course initially may resemble that of the familiar clinical picture of malignant or mechanical obstruction of the extrahepatic biliary tract, with progressively increasing jaundice and, occasionally, clay-colored stools. Phenomena suggesting an infectious origin are frequently absent. Recognition and accurate differential diagnosis are of extreme importance, since surgical exploration of the patient with acute hepatitis is associated with a high mortality. It is essential, therefore, that viral hepatitis be considered as a possibility in every jaundiced patient regardless of age.

Aside from the difficulties viral hepatitis presents in differential diagnosis, the disease, even when recognized, constitutes a further problem in management and disposition. This results from the fact that the duration of disability and incapacitation in the favorable uncomplicated overt case averages approximately six weeks. Even under the best of conditions a small percentage of patients suffer disability for longer periods as a result of the tendency of the disease to relapse, and, in a still smaller percentage, to become chronic. Although the overall mortality is low, estimated in large outbreaks as approximately 0.2 per cent, it has been as high as 20 per cent in certain small outbreaks.¹ Viral hepatitis, therefore, is never to be regarded lightly, and the initial course of the disease frequently provides no clinical warnings of an impending relapse or fatal outcome. These tendencies to natural relapse and chronicity, or fatal termination, may be exaggerated by delayed recognition and improper management. Early recognition and treatment are therefore of considerable importance. In addition, it is during the first and second weeks of jaundice that the intelligent use of a group of hepatic tests provides the most reliable and helpful assistance in differential diagnosis. All too frequently the performance of such studies early in the disease is deferred in the hope that the jaundice will subside or the cause will become obvious with the passage of time and that the patient thereby will be saved the expense and trouble of laboratory studies. The importance of obtaining a "baseline" group of hepatic tests in every jaundiced patient within the first two weeks of jaundice cannot be overemphasized. With few exceptions,

clinical phenomena cannot be depended upon for differential diagnosis, and the proper decision between medical and surgical treatment is at times life saving. For this reason, every jaundiced patient deserves prompt laboratory investigation regardless of how typical the clinical phenomena appear. As the maximum diagnostic assistance from laboratory investigations is obtained soon after jaundice is detected, failure to take advantage of such assistance at that time may be regretted later. It is not implied that laboratory tests alone will differentiate "medical" and "surgical" jaundice. Properly selected and interpreted tests applied at the right time, however, will substantially increase the incidence of correct differentiation of those two conditions or, at least, will assist in the decision concerning immediate, if not ultimate, management.

NEWER ASPECTS OF ETIOLOGY AND EPIDEMIOLOGY

The increasing medicolegal importance of viral hepatitis deserves special comment. Unfortunately, the available information indicates that a considerable, as yet unestimable, proportion of the cases of viral hepatitis are consequences of certain indispensable technics of medical practice. This is of great immediate concern to all, for it not only threatens the continued use of some of the most important and irreplaceable therapeutic weapons, blood and plasma, but also potentially involves certain costly, protracted and difficult changes in medical technic, which, ignored or not recognized, may occasionally lead to suits for malpractice.

An example is an incident, recently described in the foreign-correspondence section of the *Journal of the American Medical Association*,⁸ that resulted in the imprisonment of a physician in Italy. The justifications for the action taken in this case cannot be evaluated from the data presented, but the episode serves as a warning of the potential dangers involved.

Time does not permit a detailed discussion of this problem. It is possible only to point out, in a general way, some of the matters involved. Figure 1 represents an attempt to portray diagrammatically a tentative working concept of the etiology and epidemiology of viral hepatitis. Some of the general factors concerned in the transmission of hepatitis are as follows: blood and feces are the only proved sources of hepatitis virus, which is apparently present in high concentration, since extremely small quantities may be infectious, the viruses survive for long periods under variable conditions and resist many procedures that eliminate or inactivate most infectious agents, including desiccation, extremes of temperature, filtration, commonly used plasma preservatives (such as merthiolate) and chlorination of water under certain conditions, the virus may be present in blood or feces without previous, associated or subsequent symptoms or signs.

No extrahuman host has as yet been recognized. Therefore, discussion must at present start and end with the human host (Fig 1). Hepatitis viruses H and SH may both be acquired from human blood. Only the former has been shown to be present in the feces. Neither has been proved conclusively to be present, or absent, in urine and nasopharyngeal secretions, but present information suggests that these are not potent sources of hepatitis virus, at least during the active stages of the disease. Transmission of hepatitis virus IH from feces through one or more of the mechanisms shown in Figure 1 probably accounts

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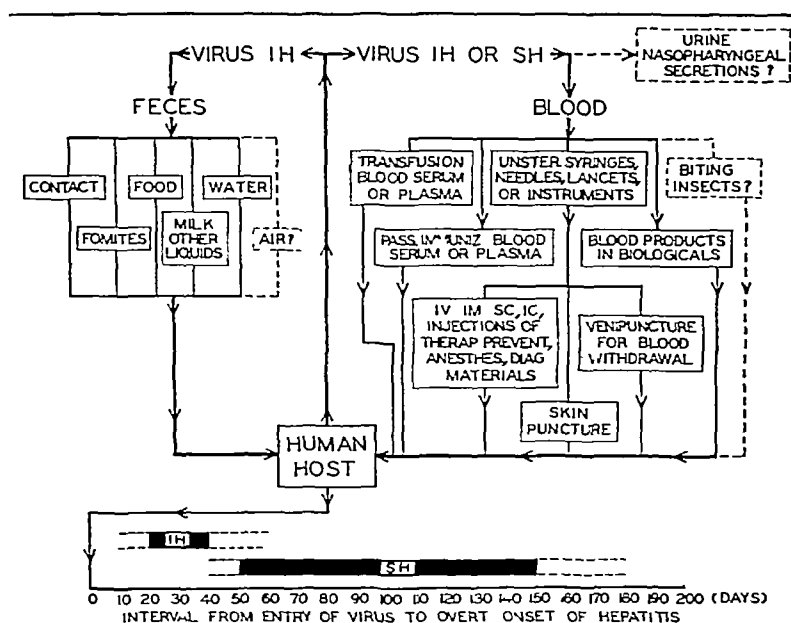


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identify the recipients and donors. Furthermore, failure to recognize and weigh the potential risk may have important medicolegal implications.

A fourth mechanism, although difficult to prove directly, is supported by a large body of epidemiologic evidence.⁹⁻²² It must therefore be recognized that the hepatitis virus may be transmitted by means of improperly sterilized syringes, needles, lancets and other instruments that have been in contact with human blood (Fig 1). As such transmission is preventable, all practical precautions must be taken. Although it is difficult and perhaps impossible to prove infection of individual cases by this mechanism, failure to recognize the potentialities is again of medicolegal importance and formed the basis of the case against the Italian physician cited above. Some of the possible means by which the hepatitis virus may gain access to a person through the medium of inadequately sterilized instruments are shown in Figure 1 as sub-headings under this mechanism.

Finally, the potential role of insect bites in the transmission of these viruses in blood is mentioned (broken lines, Fig 1), although there is as yet no direct evidence of natural transmission in this way.

SUMMARY

Viral hepatitis is presented as a widespread disease of high sporadic and epidemic incidence caused by at least two, primarily hepatotropic, filterable, infectious agents whose outstanding clinical manifestation is evidence of hepatic injury with or without associated phenomena suggesting an infectious origin.

The fact that viral hepatitis involves all age groups is emphasized, and its apparently increasing frequency as a cause of jaundice in the older age groups is discussed, particularly in relation to the importance of its consideration in every jaundiced patient regardless of age and the clinical phenomena.

The public-health, military, and individual significance of the disease is stressed, with special reference to morbidity, mortality and its unfortunate relation to certain indispensable medical technics.

The increasing medicolegal importance of the disease to the practicing physician is emphasized. This new aspect has developed with the recent recognition of the potential relation between viral hepatitis and certain medical technics. This relation is illustrated by reference to a diagram summarizing the available knowledge concerning the sources of the hepatitis viruses and the mechanisms by which they are transferred from person to person. The responsibility of the physician in the interruption of certain of these potential mechanisms is indicated.

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A SURVEY OF RECENT THERAPEUTIC MEASURES IN CIRRHOSIS OF THE LIVER*

THOMAS C. CHALMERS, M.D.,† AND CHARLES S. DAVIDSON, M.D.‡

BOSTON

ELEVEN years have elapsed since Patek¹ first reported the effectiveness of a nutritious diet in the treatment of cirrhosis of the liver. On the basis of the rapidly accumulating evidence that cirrhosis can be produced in animals on a low-protein diet and prevented by the addition of certain food factors,²⁻⁵ a nutritious diet accompanied by abstinence, when there is a history of alcohol addiction, is now the accepted method of treatment. In this communication consideration is given to certain practical aspects of the dietary treatment of cirrhosis, particularly the quantity of fat allowed, the place of vitamin and specific amino acid supplements and the importance of a low-sodium diet in the control of ascites and edema. In addition a critique is presented of the more recent method of treatment of patients with esophageal varices and ascites who are not improved by dietary means alone.

A number of observers believe that fat should be restricted in the diet provided to patients with liver disease. This conception probably has arisen from the evidence that a high-fat intake hastens the appearance of cirrhosis in animals on a low-protein diet and secondly that patients with biliary-tract obstruction generally have a fatty-food intolerance. In experimental animals, however, an adequate protein diet protects the liver from the injurious effects of fat. Moreover, patients with cirrhosis rarely have a fatty-food intolerance. Indeed Patek's⁶ patients were given 175 gm. of fat a day, together with 365 gm. of carbohydrate and 140 gm. of pro-

TABLE 1. Data on the results of treatment of patients with cirrhosis of the liver. (Based on studies reported by Patek et al.⁶)

	PER CENT OF SURVIVAL	TREATED CASES	CONTROL CASES
Of 124 cases treated	61	21	21
Of 124 cases treated	61	21	21

*Based on studies reported by Patek et al.⁶

The recently reported experiences of Patek's group⁶⁻⁹ in the dietary treatment of cirrhosis are summarized in Table 1. It should be pointed out that the controls were taken from hospital admissions between the years 1920 and 1940 when other important therapeutic measures such as chemotherapy and blood transfusions were not as generally available as they have been in the last ten years. The results are nevertheless impressive and have been confirmed,⁹⁻¹¹ and in spite of the absence of a better controlled series the importance of a nutritious diet in the treatment regime seems well established.

The mere prescription of such a diet is not sufficient. A patient with cirrhosis may have severe anorexia and must be tempted with an attractive menu. He may have to be fed by attendants or maintained by tube or parenteral feeding until his appetite returns. That there is still room for improvement in the treatment of cirrhosis even under the ideal conditions of a research service is shown by the fact that only 61 of 124 cases treated by Patek's group showed clinical improvement fulfilling the following three criteria: gain in weight and strength, disappearance of ascites, edema and jaundice, and changes toward normal values of the liver-function tests.¹²

tein. This amount of fat is necessary to ensure palatability of the diet, and no ill effects were noted by Patek in his patients. Restricting the fat content to 50 gm. a day is advocated by some,^{10, 11} results in an unpalatable, low-calorie diet that discourages the patient from taking the one "medicine" really important for him — food. Thus, no restriction of fat in the diet of patients with cirrhosis seems indicated unless obesity makes a restriction in calories necessary.

The history of prolonged poor food intake, together with signs suggestive of vitamin deficiency present in some cirrhotic patients, has made the addition of vitamin supplements to most treatment regimes common. However, some doubt has been cast on the need for the administration of large quantities of purified vitamins. It is generally agreed that the liver is a storehouse for both the water-soluble and fat-soluble vitamins and that these stores are reduced in a cirrhotic liver. But the signs thought to be due to vitamin deficiency often do not respond as well to vigorous treatment as they do in patients without liver disease. It has been suggested¹² that in some patients with cirrhosis there exists an intrinsic rather than extrinsic deficiency — that is, a diminished ability of the liver to utilize the vitamins supplied to it (for example, as coenzymes). In addition, it is theoretically pos-

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identify the recipients and donors. Furthermore, failure to recognize and weigh the potential risk may have important medicolegal implications.

A fourth mechanism, although difficult to prove directly, is supported by a large body of epidemiologic evidence.⁹⁻²² It must therefore be recognized that the hepatitis virus may be transmitted by means of improperly sterilized syringes, needles, lancets and other instruments that have been in contact with human blood (Fig 1). As such transmission is preventable, all practical precautions must be taken. Although it is difficult and perhaps impossible to prove infection of individual cases by this mechanism, failure to recognize the potentialities is again of medicolegal importance and formed the basis of the case against the Italian physician cited above. Some of the possible means by which the hepatitis virus may gain access to a person through the medium of inadequately sterilized instruments are shown in Figure 1 as sub-headings under this mechanism.

Finally, the potential role of insect bites in the transmission of these viruses in blood is mentioned (broken lines, Fig 1), although there is as yet no direct evidence of natural transmission in this way.

SUMMARY

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The mere prescription of such a diet is not sufficient. A patient with cirrhosis may have severe anorexia and must be tempted with an attractive menu. He may have to be fed by attendants or maintained by tube or parenteral feeding until his appetite returns. That there is still room for improvement in the treatment of cirrhosis even under the ideal conditions of a research service is shown by the fact that only 61 of 124 cases treated by Patek's group showed clinical improvement fulfilling the following three criteria: gain in weight and strength, disappearance of ascites, edema and jaundice, and changes toward normal values of the liver-function tests.

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TABLE 1 Duration of Life in Cirrhosis of the Liver after the Onset of Ascites in 124 Treated Patients and 230 Control Cases *

PERIOD OF SURVIVAL	TREATED CASES	CONTROL CASES
One	6	6
Two	65	59
Five	50	21
	50	7

*Based on studies reported by Patek et al.⁶⁻⁸

tein. This amount of fat is necessary to ensure palatability of the diet, and no ill effects were noted by Patek in his patients. Restricting the fat content to 50 gm a day, as advocated by some,^{10, 11} results in an unpalatable, low-calorie diet that discourages the patient from taking the one "medicine" really important for him — food. Thus, no restriction of fat in the diet of patients with cirrhosis seems indicated unless obesity makes a restriction in calories necessary.

The history of prolonged poor food intake, together with signs suggestive of vitamin deficiency present in some cirrhotic patients, has made the addition of vitamin supplements to most treatment regimes common. However, some doubt has been cast on the need for the administration of large quantities of purified vitamins. It is generally agreed that the liver is a storehouse for both the water-soluble and fat-soluble vitamins and that these stores are reduced in a cirrhotic liver. But the signs thought to be due to vitamin deficiency often do not respond as well to vigorous treatment as they do in patients without liver disease. It has been suggested¹² that in some patients with cirrhosis there exists an intrinsic, rather than extrinsic, deficiency — that is, a diminished ability of the liver to utilize the vitamins supplied to it (for example, as coenzymes). In addition, it is theoretically pos-

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sible that niacin in large doses may be harmful to patients with fatty livers. Since a portion of administered niacin is excreted as the methyl derivative, the vitamin has been given to animals to hasten the development of cirrhosis on a deficient diet by reducing the effectiveness of choline and methionine.¹³ Gillman and Gillman¹⁴ found that pellagrous children with fatty livers became worse when given large quantities of vitamins, whereas

In a disease as chronic and at the same time as variable in its course as cirrhosis it is extremely difficult to assess the efficacy of a single therapeutic measure. Adequate controls are necessary, and yet many of the reports of the clinical use of methionine and choline in cirrhosis are uncontrolled.¹⁵⁻¹⁷ In four recent studies with controls^{10, 11, 18, 19} the groups given choline or methionine showed an apparent decrease in mortality rate and somewhat greater and faster improvement than those treated with a nutritious diet alone, but the size of each group was too small to be significant and the method of selecting cases not always clear. Larger numbers of patients, strictly alternated, control and treated, are necessary to eliminate effects resulting from the many uncontrolled variables encountered in such a study. Finally, a nutritious diet furnishes in itself relatively large amounts of choline and methionine. Until the science of nutrition has become exact enough to indicate all the nutrients necessary in health and disease and the precise quantities required, it seems better to supply those nutrients as food rather than purified chemicals.

If the physician cannot induce the patient to eat a nutritious diet, crude food complements such

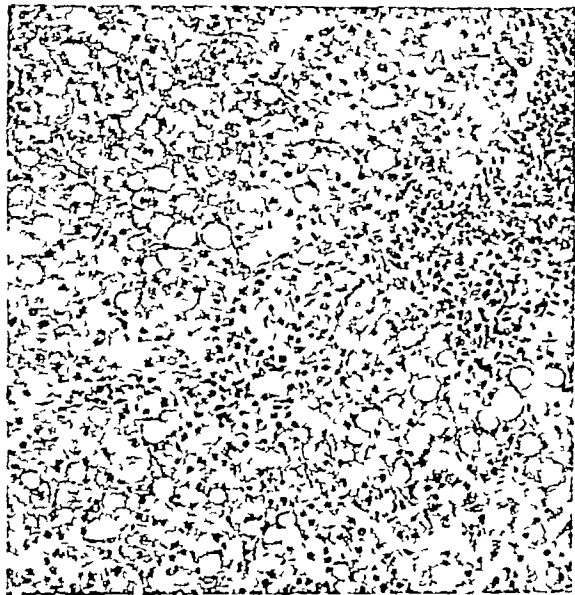


FIGURE 1 *Punch Biopsy of the Liver of a Chronic Alcoholic Patient Who Entered the Hospital Deeply Jaundiced and Close to Delirium Tremens*
There is moderate fatty metamorphosis and cellular infiltration

the fat rapidly disappeared from their livers on treatment with dried hog's stomach. They suggested that the poor results of massive vitamin therapy might be due to an antilipotropic effect of niacin. Since, therefore, large doses of the purified vitamins do not appear necessary and may be harmful, it seems wise to administer them only in the usual therapeutic quantities, or better to rely on the nutritious diet and, if necessary, crude food supplements may be given in addition.

Three nutrients that have been shown to be important in the prevention and treatment of experimental dietary liver injury in animals are choline, a source of methyl groups, and the sulfur-containing amino acids, methionine and cystine. Methionine is also an important source of methyl groups for the synthesis of choline. The exact modes of action of these substances and the possible existence of others are the subjects of present research. However, since methionine and choline have already been used rather extensively in the clinical treatment of liver disease, it is important to determine whether or not they are useful

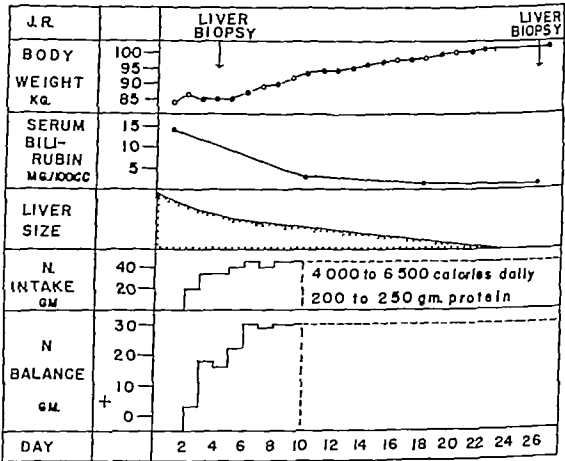


FIGURE 2 *Clinical Course of the Patient Whose Biopsies Are Shown in Figure 1 and 3*

as brewer's yeast powder, high-protein milk drinks and liver products by mouth, intramuscularly or intravenously, may be employed. Labby and his associates²⁰ reported excellent results, primarily in the form of appetite stimulation, with frequently administered intravenous crude liver extract, but here again simultaneous controls were lacking and their patients were in general of a higher economic and social stratum than the usual charity-hospital population, and thus were more amenable to all forms of therapy.

The dramatic improvement that may take place in patients with liver disease who eat well is illustrated by the course of a thirty-five-year-old longshoreman who entered the Boston City Hospital deeply jaundiced and close to delirium tremens after a prolonged drinking bout during which he ate almost nothing. A punch biopsy taken before treatment (Fig 1) shows the fatty metamorphosis characteristic of the liver cells in such patients and, in addition, a quite marked cellular infiltration around the portal areas. Figure 2 summarizes the patient's clinical course. His appetite was excellent, food intake (without supplements) was enormous, and he retained a considerable proportion of the nitrogen administered. He gained 15 kg (33 pounds), and his serum bilirubin and liver size rapidly receded to normal. Figure 3 shows his liver three weeks after therapy was begun, essentially normal. Thus early changes in the liver may be completely reversible if the patient stops drinking and eats well. This patient could hardly have im-

proved more rapidly had choline and methionine been added to his diet. The rapid recovery to be expected in early cirrhosis as contrasted with the later forms of the disease has been observed by several investigators²¹⁻²³. Indeed, it is becoming increasingly apparent that many alcoholic patients with early cirrhosis may live out their normal life span if they abstain from alcohol while continuing to eat a nutritious diet. This fact emphasizes the need for finding early cases by the freer use of sensitive liver-

function tests and punch biopsy as part of any attempt to reduce the mortality from the disease. In fact, all of 24 patients entering the Boston City Hospital with delirium tremens but without significant clinical signs of cirrhosis were found by punch biopsy to have abnormal amounts of fat in their livers and 14 to have early, asymptomatic fibrosis²⁴. Gratifying results can be obtained in this group of patients, so large in any charity hospital, if intensive treatment is instituted by the

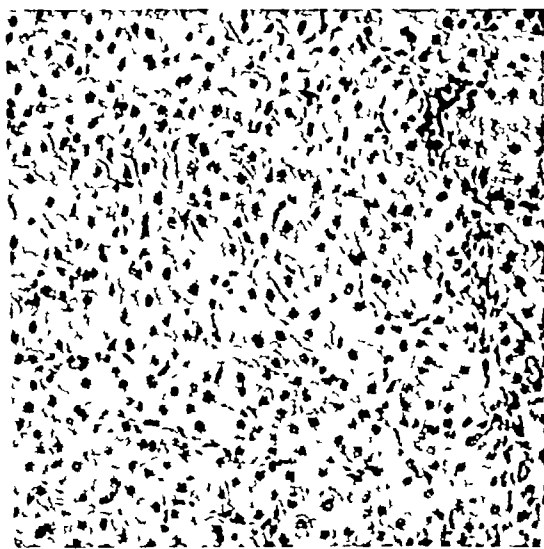


FIGURE 3 Punch Biopsy of the Liver Obtained Three Weeks after the One Illustrated in Figure 1

The fat has completely disappeared, and the biopsy is essentially normal

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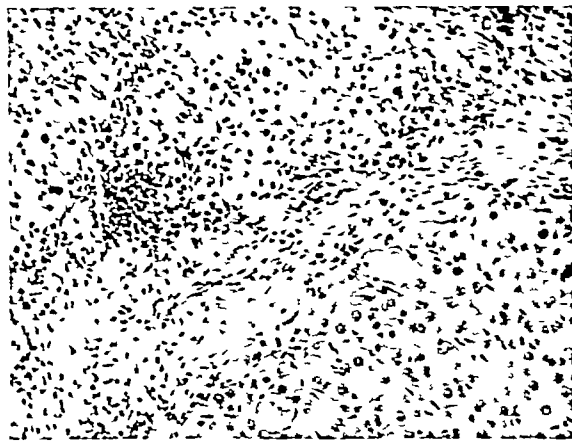


FIGURE 4 Punch Biopsy of the Liver of a Chronic Alcoholic Patient with Massive Ascites Who Had Been Treated for Three Months with a Highly Nutritious Diet

Fairly normal-appearing liver cells are encased in thick bands of fibrous tissues

combined efforts of internist, psychiatrist and social worker.

In the treatment of the more chronic forms of liver disease other problems are encountered, especially recurrent ascites. Figure 4 is a photomicrograph of a biopsy of the liver of a chronic alcoholic patient who entered the hospital with massive ascites and who for three months before biopsy required frequent paracenteses although he was treated vigorously with a nutritious diet and almost daily intravenous liver extract. The biopsy section reveals fairly normal liver cells encased in thick bands of fibrous tissue. This is the kind of stabilized patient referred to as having intractable ascites — the kind who feels and eats well but requires frequent paracenteses and who, although he may occasionally be freed of ascites, may die at any time of bleeding from ruptured esophageal varices.

How much dietary treatment can do for the patient with cirrhosis who is relatively asymptomatic except for episodes of hematemesis has not been established. It is doubtful whether diet can alter the fibrous tissue that obstructs the hepatic circulation and shifts large amounts of blood from the liver into the collaterals. Reports of such sur-

sible that niacin in large doses may be harmful to patients with fatty livers. Since a portion of administered niacin is excreted as the methyl derivative, the vitamin has been given to animals to hasten the development of cirrhosis on a deficient diet by reducing the effectiveness of choline and methionine.¹³ Gillman and Gillman¹⁴ found that pellagrous children with fatty livers became worse when given large quantities of vitamins, whereas

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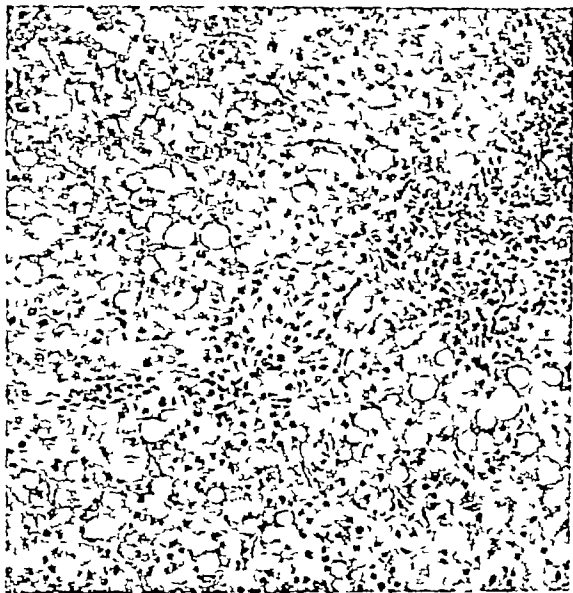


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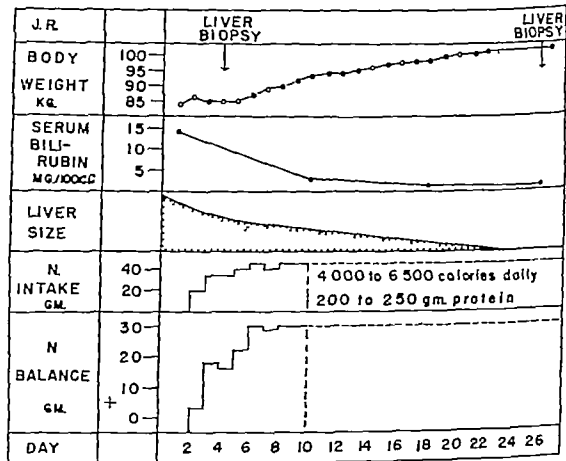


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tients were neither treated nor followed long enough*.

Responses just as erratic as those after albumin administration have been seen in patients treated with diet alone and in those given mercurial diuretics. In an effort to find a common metabolic defect altered in patients showing a response to these several measures, sodium-balance studies were performed by Faloon et al.⁴¹ The patients with decompensated cirrhosis were found to be unable to excrete administered sodium except in very small amounts. When diuresis occurred,

but with 6 gm of sodium chloride given in addition. He remained in positive sodium and water balance, gained 12 pounds in weight and required an average of 20 gm of albumin a day to maintain a normal serum albumin concentration. On withdrawal of the added 6 gm of salt his sodium balance became negative, and he stopped gaining weight and required daily only 11 gm of albumin to maintain the same serum albumin concentration.

The mechanism of this inability to excrete sodium is obscure, but the therapeutic implications are obvious. The frequency of abdominal paracentesis

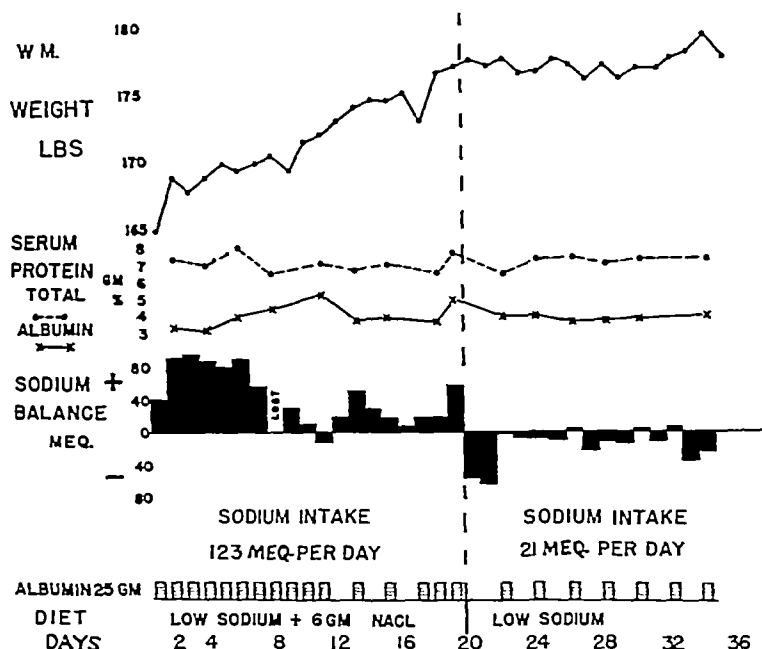


FIGURE 5 *The Effect of Sodium Restriction in the Diet of a Patient Who Is Accumulating Ascites*

The serum albumin level had previously been raised to normal by intravenous concentrated salt-poor human albumin. This was continued at a rate necessary to maintain the serum albumin at a normal level.

whether spontaneous or accompanying albumin or mercurial administration, urinary sodium rose markedly and a negative sodium balance ensued.

Figure 5 illustrates the effect of withholding salt from the diet of a patient who had required frequent paracenteses in spite of a serum protein concentration maintained at normal by the intravenous administration of albumin. Over a twenty-day period he was provided with a low-sodium diet, containing about 1.25 gm of sodium chloride a day,

*Adverse reactions that may have been associated with albumin administration were encountered in 10 patients, a third of the series reported by Faloon et al.⁴¹ Directly related to the albumin injections were 2 cases of acute pulmonary edema, 1 fatal; 1 of chill and fever followed by coma and death; 1 of fatal nosebleed and a fatal esophageal hemorrhage. One patient bled on two occasions from a gastric ulcer soon after albumin injections. Two other patients bled from ruptured esophageal varices four and seven days after albumin therapy had been stopped; both died. Two patients developed pleural effusions. It was difficult to ascertain how directly the albumin therapy contributed to these deaths. However, it is apparent that such therapy may not be without danger and should be used with caution.

can be reduced if the patient is maintained on a low-sodium diet supplemented, if desired, by ammonium chloride and mercurial diuretics. Concentrated human albumin is an expensive and in some cases perhaps a somewhat dangerous adjunct to this regime. The best results of albumin administration are seen in patients with massive edema and ascites who have not required paracentesis. The importance of restricting salt is best illustrated by the following calculations. Extrarenal loss of sodium chloride under moderate temperature conditions has been found to remain fairly constant, at about 1 gm a day.^{42, 43} Urinary loss in a cirrhotic patient who is accumulating ascites is rarely more than 0.5 gm a day, regardless of intake. If the sodium chloride intake is limited to less than 1.5 gm a day, little fluid will be retained. When the

gical procedures as injection of the esophageal collateral veins,^{24, 25} mediastinotomy²⁶ and gastrectomy²⁷ and the various operations for shunting blood from the portal to the systemic circulation²⁸⁻³⁰ are appearing in increasing numbers. Positive criteria indicating the procedure of choice are not yet available. Many more operations and controlled studies are necessary.

The results of A. H. Blakemore,³¹ who has had a large experience in the shunting operations, are illustrated in Table 2. He has tried one of several shunting procedures on 43 patients with cirrhosis with a decreasing operative mortality and an in-

have achieved good results with this operation. Optimal nutritional therapy was not usually possible after the patients left the hospital, and some of the operations were done in a rush of enthusiasm before the patients had been adequately prepared. However, patients who are abstemious and well treated by diet frequently have spontaneous remissions. The poor end results and high postoperative mortality of the patients in this series of "button" operations raise grave doubts of its value. It may be that the modification recently described by Lord³⁵ will prolong the period of relief

TABLE 2 *Results of Blood-Shunting Operations for the Relief of Ascites and Bleeding Varices in Cirrhosis of the Liver **

PURPOSE OF OPERATION	NO OF CASES	POSTOPERATIVE DEATHS	PATIENTS SURVIVING 1 YEAR OR MORE WITHOUT RECURRENCE	TOTAL DEATHS OVER 3 YEARS	RECURRENCE OF BLEEDING (MILD)	DISAPPEARANCE OF ASCITES
Ascites	6	2	2	14	2	3
Hemorrhage†	37	7 (19%)	12 (32%)	14 (38%)	2	3

*Based on personal communication from A. H. Blakemore of New York City.

†Three patients also had ascites.

creasing number of the anastomoses remaining patent. But the operation is formidable and should probably be undertaken only in patients in the best of condition. Again, this large series is still too small and the patients not followed long enough for final conclusions to be drawn.

Two years ago Crosby and Cooney³² described what appeared to be an ideal surgical method for the relief of intractable ascites. A modified Murphy button was inserted into the abdominal wall connecting the peritoneal cavity with the subcutaneous tissues, resulting in a constant emptying of ascitic fluid into the subcutaneous space whence it was returned to the circulation. The series was small, but the results were good. In contrast, the results of this procedure performed on 14 service patients from the Boston City Hospital and the Mount Auburn Hospital, Cambridge, have been poor.³³ Five patients died in the postoperative period, 6 in from three weeks to one year and 2 in from one to two years after the operation, 1 is surviving three years after operation. Of the 9 who survived the postoperative period, 4 had a recurrence of ascites within one month, 3 within three months, and 1 within fourteen months. No functioning buttons were found in the 9 autopsied patients: 4 were plugged with fibrin, and 3 with omentum, and in 5 a pseudoperitoneal cavity similar to that recently described in detail by Welch³⁴ had formed. Only 4 of the 14 patients were definitely improved for appreciable lengths of time.

It should be pointed out that this series of patients, under service rather than private care, is not directly comparable with those of others who

from ascites. No other reports of this procedure have appeared.

Recently, two significant developments have been added to the medical treatment of intractable ascites: the intravenous administration of concentrated human serum albumin, and the provision of diets low in salt. Janeway and his associates³⁵ and Thorn et al.³⁷ observed that albumin injections in doses large enough to raise the serum albumin concentration to normal induced little more than a transient diuresis. Patek and his co-workers³⁸ confirmed this in a short-term experiment. But Kunkel et al.³⁹ reported the complete disappearance of ascites in 14 of 15 patients given albumin intravenously. As might be expected, those with early ascites and generalized edema responded more readily than patients with long-standing ascites and other evidences of excessive portal obstruction.

In an effort to elucidate the reasons for these discrepancies and the mechanisms responsible for the formation and disappearance of ascites in cirrhosis, Faloon and his associates⁴⁰ studied 29 patients with ascites treated with intravenous albumin, some over long periods. Four patients had a diuresis that began soon after the first albumin administration, 7 had a delayed response, and 3 responded only after the salt content of the diet had been reduced. There were 6 failures — 6 patients who did not respond although their serum albumin concentration was maintained at between 3 and 4 gm per 100 cc for long periods. The results in 9 patients were classified as indeterminate because the pa-

tients were neither treated nor followed long enough *

Responses just as erratic as those after albumin administration have been seen in patients treated with diet alone and in those given mercurial diuretics. In an effort to find a common metabolic defect altered in patients showing a response to these several measures, sodium-balance studies were performed by Faloon et al.⁴¹ The patients with decompensated cirrhosis were found to be unable to excrete administered sodium except in very small amounts. When diuresis occurred,

but with 6 gm of sodium chloride given in addition. He remained in positive sodium and water balance, gained 12 pounds in weight and required an average of 20 gm of albumin a day to maintain a normal serum albumin concentration. On withdrawal of the added 6 gm of salt his sodium balance became negative, and he stopped gaining weight and required daily only 11 gm of albumin to maintain the same serum albumin concentration.

The mechanism of this inability to excrete sodium is obscure, but the therapeutic implications are obvious. The frequency of abdominal paracentesis

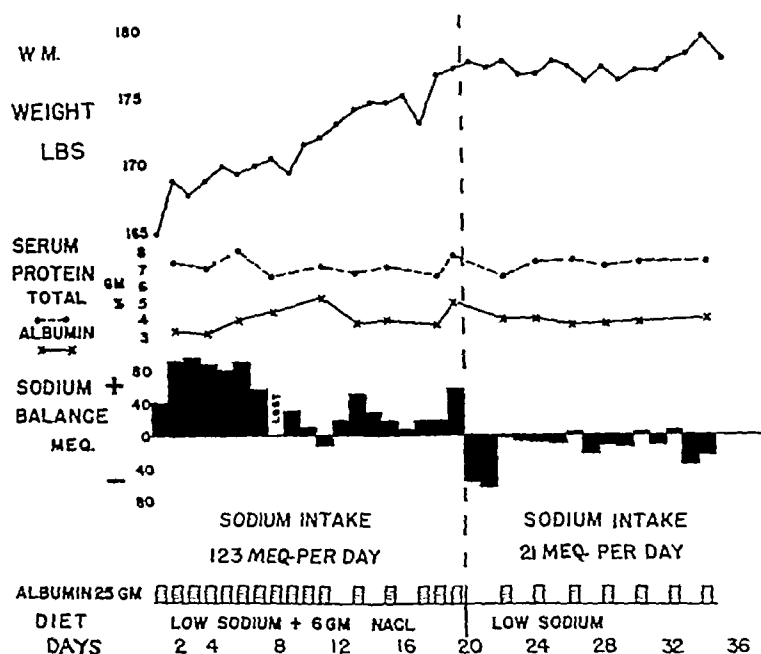


FIGURE 5 The Effect of Sodium Restriction in the Diet of a Patient Who Is Accumulating Ascites

The serum albumin level had previously been raised to normal by intravenous concentrated salt-poor human albumin. This was continued at a rate necessary to maintain the serum albumin at a normal level.

whether spontaneous or accompanying albumin or mercurial administration, urinary sodium rose markedly and a negative sodium balance ensued.

Figure 5 illustrates the effect of withholding salt from the diet of a patient who had required frequent paracenteses in spite of a serum protein concentration maintained at normal by the intravenous administration of albumin. Over a twenty-day period he was provided with a low-sodium diet, containing about 1.25 gm of sodium chloride a day,

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intake is 6 gm, as in the ordinary hospital diet without added salt, around 500 cc may be retained When the intake is 10 gm, as in the usual American diet salted to taste, approximately a liter of fluid, equal to 2 pounds of body weight, may be retained a day

Patients with ascites have not generally been treated with a low-salt diet in the past because it is difficult to prepare a nutritious diet, particularly one adequate in protein, which is at the same time low in salt The diet employed by Faloon et al, presented in Table 3, contains only approximately

There is general agreement that it is one of the most important therapeutic measures, as pointed out by Jones and Volwiler⁴⁴ in their review of the treatment of chronic hepatitis This clinical observation is supported by the experimental work of Bradley⁴⁵ on the relation of posture to hepatic blood flow

SUMMARY

The employment of a palatable, nutritious diet adequate in protein and not reduced in fat content

TABLE 3 Nutritious Diet Low in Sodium *

FOOD	AMOUNT	HOUSEHOLD MEASURES	CARBOHYDRATE	PROTEIN	FAT	SODIUM
	gm		gm	gm	gm.	mg
Breakfast						
Orange	100	1 (medium)	11 2	0 9	0 2	0 2
Shredded wheat	30	1 biscuit	23 6	3 1	0 4	0 6
Bread	50	2 slices	25 0	4 0	2 0	1 0
Butter	20	2 pats	—	0 2	16 2	1 0
Egg	50	1 egg	0 4	6 4	5 8	70 0
Cream (light)	100	3 ounces	4 0	2 9½	20 0	52 0
Sugar	25	2 tablespoonfuls	25 0	—	—	—
Low sodium milk	150	4 glasses per day	57 0	40 5	42 0	15 0
Dinner						
Beef	100	3¼ ounces	—	23 1	7 6	53 0
Potato	100	¾ cup	19 1	2 0	0 1	0 6
Carrots	100	¾ cup	9 3	1 2	0 3	31 0
Beans	100	¾ cup	7 7	2 4	0 2	0 8
Bread	50	2 slices	25 0	4 0	2 0	1 0
Butter	20	2 pats	—	0 2	16 2	1 0
Bananas	150	1 (large)	34 5	1 8	0 3	0 2
Supper						
Chicken	100	¼ breast	—	26 2	10 4	94 0
Peas	100	¾ cup	17 7	6 7	0 4	0 9
Tomatoes	100	1 (medium)	4 0	1 0	0 3	3 0
Bread	50	2 slices	25 0	4 0	2 0	1 0
Butter	20	2 pats	—	0 2	16 2	1 0
Peaches (canned)	100	2 halves	18 2	0 4	0 1	6 0
Totals			306 7	131 2	142 7	333 3

*This diet which was compiled by Miss Kathleen A. Clinton dietitian at the Thorndike Memorial Laboratory, contains approximately 3000 calories and 330 mg of sodium or 835 mg of sodium chloride. Caloric values were calculated from standard food tables. Sodium values were taken from *Sodium and Potassium Analyses of Foods and Waters* (fifth list), Mead Johnson and Company, Evansville, Indiana, and *The Chemical Composition of Foods* (second edition) by R. A. McCance and E. M. Widdowson (Brooklyn: Chemical Publishing Co. 1947).

Fresh fruits and vegetables should be used. Butter must be sweet or washed. Bread must be salt poor and may be obtained at some bakeries or made at home with salt poor flour and low sodium milk powder instead of whole milk. Cottage cheese is the only cheese allowed but should be washed. Processed, canned or smoked meats should not be used. Low-sodium milk powder (Lonalac) may be obtained from Mead Johnson & Company. Cereals allowed: Farina, plain Wheatena, Instant Ralston Maltex Oatmeal (rolled oats), Puffed Rice, Puffed Wheat and Shredded Wheat. Many quick-cooking cereals and dry cereals are high in salt.

0.8 gm of sodium chloride, but there are 131 gm of protein, 309 gm of carbohydrate and 143 gm of fat—approximately 3000 calories. The salt content is kept low by the use of bread of low-salt content, sweet butter, vegetables cooked or canned without added salt and a low-sodium milk powder, or other low-sodium protein supplement. The taste of the diet may be improved by the employment of a salt substitute—one in which the sodium, not the chloride ion, is replaced. No untoward symptoms due to sodium or chloride deprivation were noted in this study, which was performed in the winter months, but such symptoms might develop during the hot summer months in patients being maintained free of ascites on a low-salt diet.

Finally, the importance of bed rest in the treatment of chronic hepatic disease should be mentioned

has, with chemotherapy and blood transfusions, improved the prognosis of hepatic cirrhosis.

Such nutrients as vitamins, methionine and choline are probably supplied in adequate amounts by the nutritious diet described. If food cannot be taken in a sufficient quantity, crude food complements should be administered.

The role of surgery in the treatment of portal hypertension is still not established, but it seems probable that the mortality from ruptured esophageal varices may be reduced by procedures such as portal-systemic venous anastomosis.

Intractable ascites is best treated by a nutritious diet, low in salt, supplemented by mercurial and other diuretics and, if necessary, by intravenously administered, salt-poor, concentrated serum albumin.

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VARIATIONS IN HEPATIC BLOOD FLOW IN MAN DURING HEALTH AND DISEASE*

STANLEY E. BRADLEY, M.D.†

NEW YORK CITY

THE liver acts as a selective barrier between the gastrointestinal tract and the systemic circulation, metabolizing, detoxifying and elaborating for further physiologic disposition various substances that enter the portal blood during digestion. Unquestionably, the rich and complex vasculature of the liver serves these processes by providing an adequate supply of oxygen and raw materials. In

of data obtained under these circumstances and prevent quantitative evaluation of discrete parenchymal activities.

The recent development of methods for the atraumatic catheterization of the great veins by Cournand and his co-workers¹ at Bellevue Hospital has provided a means by which hepatic venous blood may be sampled at frequent intervals in human subjects without difficulty. By this method a long, radio-opaque ureteral catheter may be inserted into an antecubital vein, and passed under fluoroscopic control through the superior vena cava and right atrium into the inferior vena cava and thence into one of the right hepatic veins (Fig 1). Blood may then be withdrawn through the catheter as desired. A vast new field of study has thus been opened to exploration. The hepatic extraction of various substances may be measured directly, and hepatic blood flow may be estimated by a clearance technic.² Bromsulfalein (BSP) has been used for the latter purpose since it is removed from the blood almost exclusively by the liver.³ Hence it seems reasonable to assume that the rate of intravenous infusion of BSP is equal to the rate of hepatic BSP removal when the BSP concentration in the blood is kept constant. Dividing the calculated rate of removal by the difference between BSP concentrations in hepatic venous and peripheral arterial (or venous) blood will yield a value approximating hepatic blood flow. The principle of this procedure is familiar as the basis of the methods by which cardiac output and renal blood flow are measured. Since the dye may be removed to a certain extent by tissues outside the liver, since the concentration in peripheral arterial blood may not equal the concentration in the portal vein, and since the blood coming from only one hepatic vein is sampled and may not therefore be representative of the liver as a whole, the figure for hepatic blood flow has been referred to as "estimated hepatic blood flow" (EHBF). However, values given by this method are in agreement with those obtained by other procedures⁴ not open to these particular errors and may be considered valid measures of the hepatic circulation. It is evident, however, that EHBF is a measure of volume of blood flowing into the splanchnic vasculature each minute, without reference to the relative contributions of the mesenteric, splenic, gastric and hepatic arterial inflows.

In 50 normal resting human subjects studied at the Evans Memorial Hospital in Boston, EHBF ranged from 950 to 1840 cc per minute per 1.73 M² of body surface, averaging 1490 cc per minute



FIGURE 1 Catheterization of the Hepatic Veins

In this skiagraph, the radio-opaque catheter may be seen passing through the right axillary and subclavian veins to the superior vena cava and thence through the right atrium and upper portion of the inferior vena cava to a vein in the right lobe of the liver.

addition, this extensive vascularity itself may indicate an important role in cardiovascular dynamics.

Unfortunately, very little is known about the physiology of the hepatic circulation, largely because it is so inaccessible. Traumatic surgical manipulations required for its study are obviously inapplicable in the study of man and are open to serious question when used in the study of animals. Gross distortions of function arising from operative injury and anesthesia complicate the interpretation

*From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the Presbyterian Hospital.

†Assistant professor of medicine, Columbia University College of Physicians and Surgeons; assistant attending physician, Presbyterian Hospital.

Thus, approximately 25 per cent of the basal cardiac output appears to pass through the splanchnic circuit. The kidneys and the brain also receive large amounts of blood, approximately 1200 cc passing through the kidneys⁵ and 800 cc through the brain,⁶ on the average, each minute. Since the cerebral circulation must be kept constant within relatively narrow limits it is obvious that the major task of vascular regulation must fall upon the liver and kidneys. Numerous studies⁷⁻¹⁰ have demonstrated conclusively that the renal blood flow is highly variable and quickly adjusted to current requirements in such a manner as to maintain arterial pressure and to compensate for relatively inadequate responses of cardiac output as in chronic anemia or orthostasis. Indeed, this activity may be carried to such an extreme that irreversible renal damage may occur after prolonged intrarenal vasoconstriction during shock. Studies of the hepatic circulation indicate that the liver also plays a prominent role in vascular homeostasis.

In animal experiments, a remarkable variation in hepatic blood flow has been observed, ranging in one study¹¹ from 40 to 160 cc per minute per 100 gm of liver tissue. The variability has been attributed to irregularity of blood flow through the sinusoids. Direct observation of the transilluminated liver has revealed free flow of blood through only about a quarter of the sinusoids at any moment, owing to intermittent passage through individual vessels.¹² With hyperemia, a larger number of sinusoids open to permit passage of a correspondingly larger volume of blood, whereas during hepatic ischemia intermittency becomes more marked. In human subjects the range of blood flow was relatively large, but it was by no means of this magnitude and appeared indeed chiefly a function of the errors inherent in the method of measurement. Moreover, the values for BSP extraction by different parts of the liver agreed fairly closely. Hence it appears that blood is distributed evenly throughout the liver and that changes in blood flow may be attributed to diffuse rather than to gross focal alterations in vasomotor activity. Of course, it is impossible to say whether vasomotor activity responsible for changes in EHBF also affects the splanchnic arterioles, but it seems wholly likely that it does, since vasoconstriction in the liver alone would operate to impound blood in the portal area with detrimental effect upon systemic hemodynamics. Exclusively hepatic vasodilation would produce the same effect by raising the pressure in the hepatic arterial capillaries, with a resulting dynamic obstruction to portal venous outflow.

A study of hepatic circulatory dynamics during exercise was undertaken in collaboration with Dr E. DeF. Baldwin at the Columbia-Presbyterian Medical Center for the purpose of assessing integration of the hepatic circulation into the total circulatory system during stress. Simultaneous measure-

ments of cardiac output (by the direct Fick method), renal blood flow (by the sodium p-amino hippurate clearance) and hepatic blood flow (by BSP clearance) were made in normal volunteers prior to and during exercise, which consisted of bicycling against weights in the recumbent position. The findings during such a study are presented in Figure 2. Blood-pressure recordings, measured in another person under similar circumstances, have been inserted in Figure 2 to provide a complete

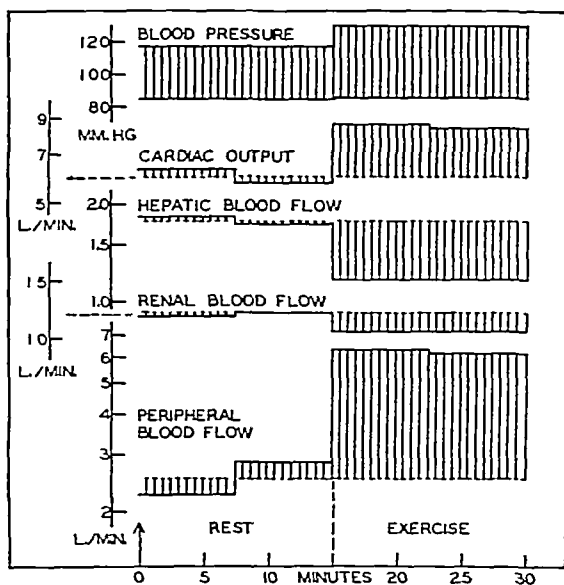


FIGURE 2 Effect of Exercise on Estimated Hepatic Blood Flow, Renal Blood Flow, Peripheral Blood Flow and Arterial Pressure in Man

With the exception of the arterial pressure, which was measured sphygmomanometrically in a separate study, all determinations were made as nearly simultaneously as possible under standard conditions. The sum of the values for estimated hepatic blood flow (bromsulfalein method) and effective renal blood flow (sodium p-aminohippurate clearance corrected for the hematocrit) was subtracted from the cardiac output (direct Fick method) to obtain a figure for peripheral blood flow. Exercise (bicycling against weights in recumbency) was started thirty minutes after the beginning of the study. Cardiac output increased, but blood flow through the renal and hepatportal circuits fell, thus permitting a considerably larger increment in blood flow to the periphery than would have been possible on the basis of the change in cardiac output alone.

picture of hemodynamic events. Although little change in blood pressure occurred during exercise the output of the heart almost doubled. At the same time the blood flow through the kidney and the liver (that is, the splanchnic vascular bed) fell sharply, the hepatic blood flow to a much greater extent than the renal. The blood flow to other circuits — the brain, heart and especially the muscles — thus increased to a greater extent than is indicated by the change in cardiac output. In this way blood was made available at the expense of the liver and kidneys, while the heart was spared

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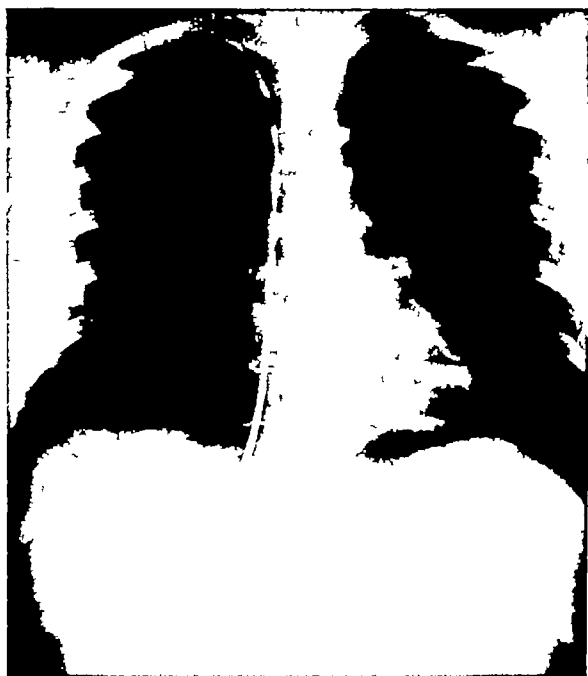


FIGURE 1 Catheterization of the Hepatic Veins

In this skiagraph, the radio-opaque catheter may be seen passing through the right axillary and subclavian veins to the superior vena cava and thence through the right atrium and upper portion of the inferior vena cava to a vein in the right lobe of the liver.

addition, this extensive vascularity itself may indicate an important role in cardiovascular dynamics.

Unfortunately, very little is known about the physiology of the hepatic circulation, largely because it is so inaccessible. Traumatic surgical manipulations required for its study are obviously inapplicable in the study of man and are open to serious question when used in the study of animals. Gross distortions of function arising from operative injury and anesthesia complicate the interpretation

*From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the Presbyterian Hospital.

†Assistant professor of medicine, Columbia University College of Physicians and Surgeons; assistant attending physician, Presbyterian Hospital.

demonstrable for a period of at least twenty-four hours after the onset of the reaction. It is not so well known, perhaps, that pyrogen may have such an effect even when fever does not develop. In a clinical investigation of this factor¹⁷ typhoid vaccine was administered to patients undergoing fever therapy, after premedication with aminopyrine. As a result, the body temperature remained unchanged, but the physiologic response was otherwise unaltered. In 2 of 8 subjects, slight tender enlargement of the liver was demonstrable, there was an increase in serum alkaline phosphatase, and the cephalin-cholesterol flocculation test became positive, reverting to normal in a few days. In these subjects the detrimental effect of the pyrogenic

Beautiful plastic reconstructions have been made by the introduction of an injection mass of celloidin, neoprene or other materials under pressure into the hepatic artery and portal veins, permitting it to harden and then carefully digesting away the parenchymal tissue, as demonstrated by McIndoe.¹⁸ These models show in a most convincing and graphic manner how Laennec's cirrhosis affects the blood

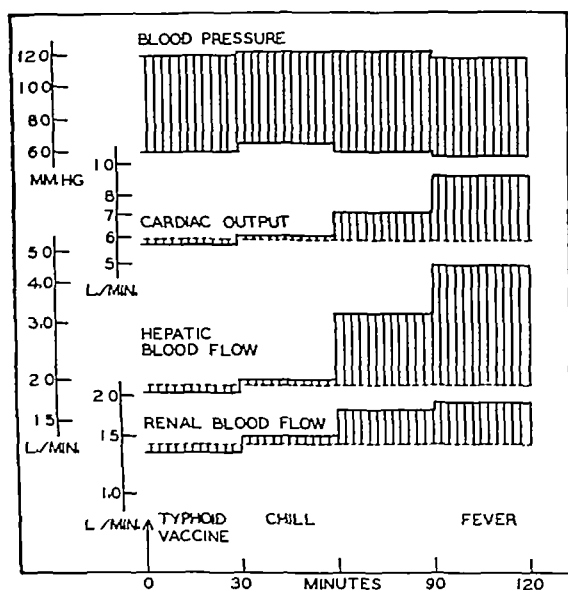


FIGURE 4 Effect of the Pyrogenic Reaction upon Arterial Pressure, Cardiac Output, Estimated Hepatic Blood Flow and Renal Blood Flow in Man

Results from two studies, one in which hepatic blood flow was determined after intravenous administration of typhoid vaccine (100 000,000 organisms) and a second in which arterial pressure, cardiac output (ballistocardiograph) and renal blood flow were measured after a dose of pyrogenic inulin (100 mg intravenously) are combined in this graph. For the sake of convenience the pyrogen is noted here only as "typhoid vaccine." During pyrexia, hepatic hyperemia develops in association with renal hyperemia as the cardiac output increases.

substance was evident despite the absence of fever. It is a very short step indeed to the inference that similar reactions with or without fever would be undesirable — perhaps even disastrous — during convalescence from inflammatory hepatic disease.

Disturbances of hepatic blood flow may be expected to result from the structural disorganization following severe injury by toxic agents or infection. Cirrhosis, in particular, is associated with a striking deformation of the hepatic blood vessels

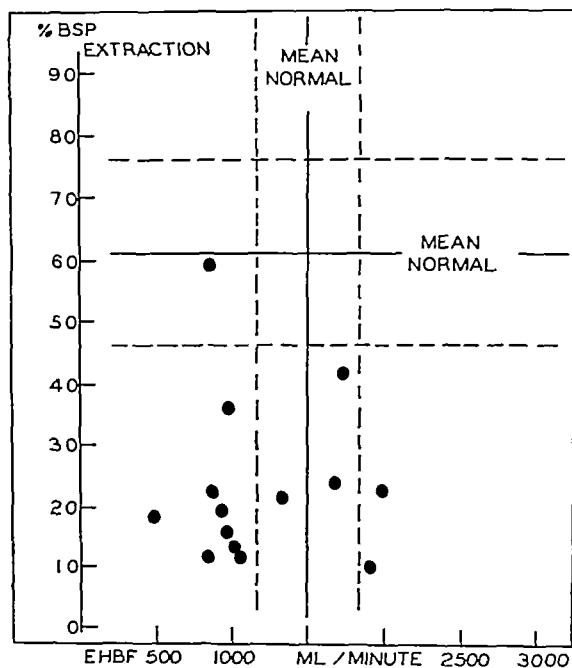


FIGURE 5 Estimated Hepatic Blood Flow (EHBF) and Bromsulfalein (BSP) Excretion in Cirrhosis of the Liver

vessels of the liver. One can see at a glance the simplification, reduction and distortion of both arterial and portal venous radicles, in sharp contrast to the complex and massive arrangement of the innumerable interwoven vessels of the normal. On anatomic grounds alone one would almost certainly say that hepatic blood flow is reduced. Nonetheless, in the absence of supporting functional evidence, the question has remained open since vasodilation or shunting, even in such a circulatory bed as this, might result in hyperemia. Indeed, evidence has been brought forward in support of the claim that the hepatic outflow may be augmented, rather than reduced, perhaps chiefly as a result of enhanced arterial inflow, which may impose a dynamic resistance to portal venous inflow and contribute to the elevation of portal pressure. Thus, in 1907 Herrick¹⁹ found that the hepatic artery may be perfused with saline solution in the liver removed after death, more easily in the cirrhotic than in the normal person. And Dock,²⁰ more recently, has found decreased arterial resistance to

the effort required to expel sufficient blood to meet the total need imposed by exercising muscle

The subjects of this investigation were placed under the stress of exercise alone as far as it was possible. Hence they were maintained in the recumbent position throughout. The upright position imposes an independent burden upon the circulation and if coupled with exercise might

right position (with the use of a tilt-table) are compared with figures for cardiac output (obtained by Dr André Cournand) and renal blood flow (taken from figures published by H W Smith⁷) determined in other normal subjects under similar conditions. It is evident that the hepatic and renal hemodynamic adjustments were similar to those observed in response to exercise, whereas cardiac output was reduced by gravitational interference with the return of blood to the heart. Hence, the hepatic and splanchnic vasoconstriction implicit in the reduction of blood flow in spite of an elevated mean arterial pressure operate to maintain blood flow to areas more sensitive to the effects of ischemia.

What bearing may these findings have upon understanding of disease of the liver? Obviously, any attempt to answer this question enters the realm of speculation. The only conclusions we are entitled to draw from these observations relate exclusively to normal man and throw light only upon normal regulatory mechanisms. Nonetheless, the temptation is irresistible, and with this warning it is perhaps permissible to make certain tentative inferences. There is growing agreement that convalescence from inflammatory hepatic disease and, in particular, from infectious hepatitis is disturbed by early mobilization and return to activity.^{14, 15} Since an adequate supply of blood is usually essential in hastening and maintaining the repair of damaged tissue, and since ordinary activity involves exertion in the upright position, it is possible that the vasoconstriction demonstrable in these studies is one of the factors involved in causing relapse and retarding recovery.

Another factor that comes to mind in such speculations is the possible influence of minor febrile infections. Fever has been shown¹⁶ to produce a striking physiologic disturbance that affects nearly every organ system in the body. The response of the cardiovascular system during pyrogenic reactions is particularly striking, and it is not surprising therefore to find that the hepatic vasculature participates actively in these readjustments.

A composite picture of the typical circulatory events observed during the pyrogenic reaction in 2 normal subjects is presented in Figure 4. Hepatic blood flow was determined in 1, and cardiac output, arterial pressure and renal blood flow in the other. The marked increase in vascular activity is clearly evident. Cardiac output increased after the chill phase in association with increased blood flow through both kidney and liver. The increment in cardiac output appears to be accounted for in large part by the augmentation in renal and hepatic blood flow. Of considerable interest is the appearance of hepatocellular dysfunction, which was evident in the marked depression of the extraction of BSP from the blood perfusing the liver. Brom-sulfalein was no longer efficiently eliminated from the blood by the liver, and retention of BSP was

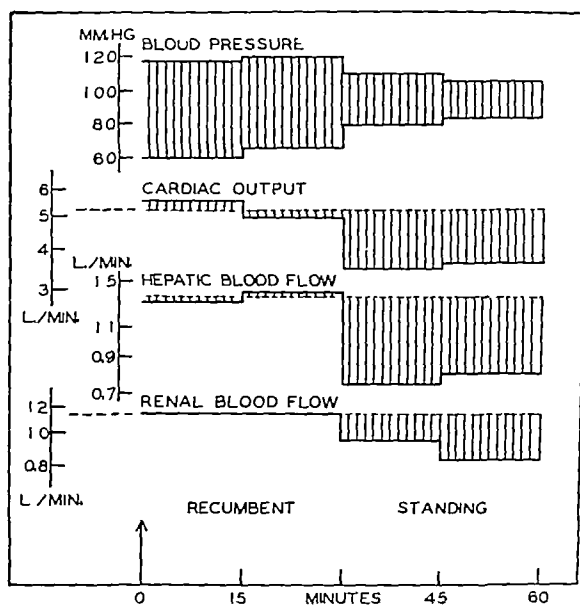


FIGURE 3 Effect of Standing Upright upon Arterial Pressure, Cardiac Output, Estimated Hepatic Blood Flow and Renal Blood Flow in Man

This composite picture of the vascular readjustments after a change in position from recumbency to standing by means of a tilt-table is based upon figures for arterial pressure (Hamilton manometer) and estimated hepatic blood flow determined simultaneously in one patient and for cardiac output (provided through the courtesy of Dr André Cournand) and renal blood flow (Chasis et al.⁷) obtained in other patients under similar conditions. Since cardiac output was not measured at the same time as renal and hepatic blood flow, the peripheral blood flow could not be calculated. With the postural change there was a fall in cardiac output without much change in mean arterial pressure although the pulse pressure decreased, apparently as a result of diminished stroke volume. Vasoconstriction in the hepatoportal and renal vascular beds apparently contributes to the increased total peripheral vascular resistance implicit in this phenomenon, thus accounting for the reduction in local flows despite maintenance of arterial pressure.

be expected to influence the picture and make interpretation difficult. It seemed of great interest to know whether standing alters the hepatic circulation as much as it affects the total circulation, and so a study of the question was undertaken at the Evans Memorial Hospital in Boston.¹³ These workers have investigated the question very thoroughly, and there is little reason to doubt the accuracy of the synthesis presented here. In Figure 3, arterial pressure measured with the Hamilton membrane manometer and hepatic blood flow determined before and after assumption of the up-

There is little doubt that this obstruction is largely responsible for the elevation in the portal venous pressure, and for the sequelae of that portentous development.

In this discussion an attempt has been made to indicate an approach to the detailed analysis of hepatic function and dysfunction in man. On the basis of the studies described here and those of many other workers one can assign to the liver a role of importance not only in metabolic activities but also in cardiovascular dynamics, since it provides, with the kidney, a kind of hemodynamic buffer against undue stress. Although the implications of this concept are not yet completely explored, it is evident that the hepatoportal circulation has become a matter of more than passing interest to students of cardiovascular physiology and disease.

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POST-PARTUM HEMATOMA*

ARTHUR W. LYONS, M.D.†

LAWRENCE, MASSACHUSETTS

IN REVIEWING discussions on intra-partum and post-partum complications in the obstetric textbooks one finds little space allotted to hematomas. A survey of the literature discloses 188 cases of paravaginal hematoma reported from 1554 to 1948. The incidence varies from 1/1951 deliveries reported by Moschkow¹ to 1/7000 by De Lee². The immediate vulvar type is the most common. In a review of 1250 deliveries 3 cases of hematoma were found: the first was vulvar, requiring removal of episiotomy sutures, evacuation of the clot and resuturing two hours after delivery; the second was vulvar, requiring removal of sutures, evacuation of the clot and resuture twenty-four hours after delivery; and the third, which was of the late paravaginal type, is reported below. Another group that has been separately reported is the retroperitoneal. Williams³ reviewed 33 cases of this kind, 22 occurring prior to 1880, with a mortality of 73

per cent. De Lee² states that the mortality in this type was 40 per cent prior to the institution of active treatment. Hamilton⁴ reported a mortality of 83 per cent since the introduction of active treatment, and Frank-Kamenetsky⁵ one of 93 per cent.

Obstetric hematomas, then, may be vulvar, paravaginal, intraligamentary or retroperitoneal, or a combination of these locations. The vulvar type appears immediately or within a few hours after delivery, the bleeding vessel being located external to the pelvic fascia and levators. Later, a blue, sensitive, elastic mass appears, and the diagnosis is made on inspection and palpation. The paravaginal type may be unnoticed for some time. The patient complains of increasingly severe pain, "bearing-down" pains or rectal discomfort. On examination a mass may be found in the vaginal wall projecting into the vagina. On rectal examination a mass may be palpated. This is the type that can dissect upward beneath Poupert's ligament, into the broad ligament, and retroperitoneally to the diaphragm. Finally, with massive hemorrhage,

*From the Obstetrical and Gynecological services, Bon Secours Hospital, Baltimore, Maryland.

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perfusion with kerosene in alcoholic cirrhosis, but not in other types of the disorder. Obviously, such post-mortem changes may have no bearing on events during life. Hence, in collaboration with Dr F J Ingelfinger, in Boston, and Drs A E Groff and G P Bradley, in New York, hepatic blood flow was estimated in a group of patients with well established Laennec's cirrhosis and chronic alcoholism, and in 3 persons with cirrhosis due to periportal fibrosis, schistosomiasis and syphilis, respectively.²¹ The results of this study are summarized in Figure 5, from which values obtained in patients who ex-

is particularly interesting. It may indicate arteriovenous shunting, perfusion of a large mass of non-extracting scar tissue or failure of damaged parenchymal cells to remove the dye from blood passing through the liver. Studies of hepatic oxygen excretion were made to assess the relative importance of these possibilities.

In Figure 6, the values for hepatic oxygen arteriovenous concentration differences are plotted against those for hepatic venous oxygen saturation in normal subjects and patients with cirrhosis. It may be seen that, with one exception, the hepatic oxygen arteriovenous difference in cirrhotic patients exceeded the normal range, and in most cases there was evidence of increased hepatic venous unsaturation. However, splanchnic oxygen consumption did not increase, for the increment in hepatic oxygen arteriovenous difference usually failed even to compensate for the reduction in blood flow, so that oxygen consumption tended to fall. These changes would be expected to follow a reduction in the mass of operative parenchymal tissue associated with maintenance of oxygen consumption per unit mass of residual tissue, at a relatively constant level. In the kidney, the oxygen arteriovenous difference tends to remain within narrow limits despite wide fluctuations in blood flow, indicating variation of oxygen consumption by renal tissue as a function of blood flow. The liver appears to differ radically from the kidney in this respect since oxygen excretion rises when blood flow through the liver is decreased during standing,^{22, 23} and it therefore seems reasonable to ascribe increased hepatoportal oxygen excretion during cirrhosis to a more sluggish flow of blood through active tissues. Continued normal oxygen uptake by the intestines and spleen from a smaller volume of blood may account in part for the change in hepatic arteriovenous difference. But the portal arteriovenous oxygen difference is small (0.93 vol per cent in each of 2 patients with cirrhosis and portal hypertension at operation), and the hepatic arteriovenous difference may be high in cirrhosis after ligation of the portal vein.²⁴ It may be inferred, therefore, that hepatic tissue is the most important site of oxygen uptake and that augmented oxygen excretion indicates relative ischemia of hepatic parenchyma. Hence, it appears on functional grounds that hepatic flow is greatly reduced in cirrhosis of the liver, regardless of etiology, as a result of an increased vascular resistance that acts to produce a relative ischemia of hepatic tissues, in which excretive—that is, parenchymal—cells figure much less prominently than in the normal organ. These observations are consistent with the view that fibrotic contraction impedes the flow of blood through the liver and that parenchymal injury thus has primacy in production of the structural changes of cirrhosis. Nonetheless, it is likely that the obstruction to blood flow may perpetuate and exaggerate the fundamental lesion

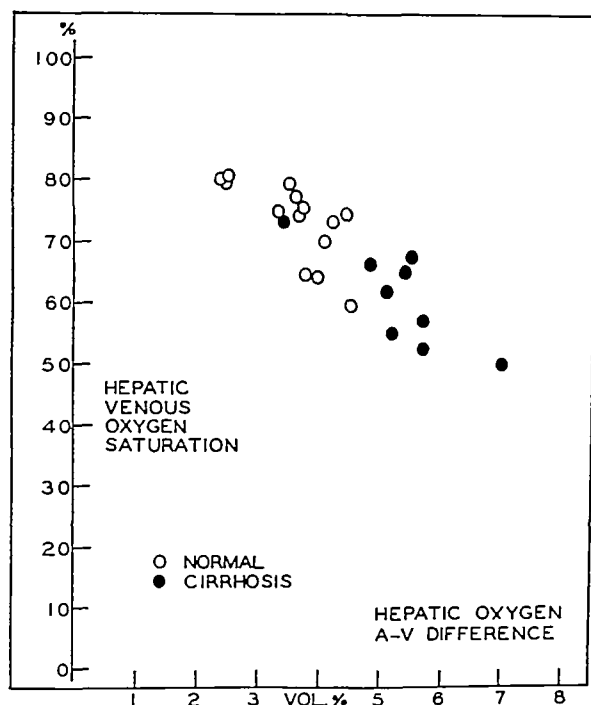


FIGURE 6 *Hepatic Oxygen Arteriovenous Difference and Hepatic Venous Oxygen Saturation in Cirrhosis of the Liver*. With one exception the values for hepatic oxygen arteriovenous difference were depressed in cirrhosis (closed circles) below the normal values (open circles). There was an associated but less striking reduction in hepatic venous oxygen saturation.

creted less than 10 per cent of BSP have been excluded. In only 4 subjects did the value for blood flow exceed the normal mean value of EHBf.

In 9, EHBf fell below the lowest normal figure. It should be noted that the values for hepatic blood flow are subject to error as result of the marked depression in the ability of the liver to remove BSP in all but 1 member of this series. Such an error would result in falsely high values for EHBf since the removal of BSP by extrahepatic tissues would contribute disproportionately to the total calculated removal rate. Hence the low values actually observed are the more significant of a true reduction in blood flow. The reduction in BSP excretion

There is little doubt that this obstruction is largely responsible for the elevation in the portal venous pressure, and for the sequelae of that portentous development

In this discussion an attempt has been made to indicate an approach to the detailed analysis of hepatic function and dysfunction in man. On the basis of the studies described here and those of many other workers one can assign to the liver a role of importance not only in metabolic activities but also in cardiovascular dynamics, since it provides, with the kidney, a kind of hemodynamic buffer against undue stress. Although the implications of this concept are not yet completely explored, it is evident that the hepatoportal circulation has become a matter of more than passing interest to students of cardiovascular physiology and disease.

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the patient exhibits signs of shock, necessitating immediate supportive measures

The etiology of this complication is quite apparent when one considers the progress of the fetus through the birth canal, subjecting the maternal tissue to long-standing contusing and avulsing trauma. And it is generally agreed that the immediate type is caused by trauma, which De Lee,² Hamilton⁴ and others list as the major causal factor. The late type is attributed to pressure necrosis of vessels caused by prolonged compression by the fetal head. Also listed as causes are laceration of inelastic vessels, toxemias, the presence of a blood dyscrasia and varicosities. Even slight trauma may activate these cases. Lacomme⁶ believes that hematomas may occur more frequently in the young primipara. The logic is apparent—the canal has not been previously dilated, and there is more tissue resistance. In general it may be said that the early hematomas are due to trauma and the late ones to pressure necrosis.

The diagnosis is made on the bluish discoloration, tumefaction and pain. Inspection and examination of any patient complaining of severe, continuous pain after delivery is mandatory. All reviewers stress the fact that cases are missed because the attending physician attributes the complaint of pain to episiotomy sutures. In the subperitoneal hematoma, tearing, labor-like pain continues, a high fundus is found, and early shock occurs.

Treatment should be prophylactic so far as possible. An episiotomy and the use of outlet forceps will help prevent vulvar damage, especially in young primiparas. A thorough inspection for tears and good tissue approximation are essential. Michaels and Herring⁷ stress the importance of the repair, stating that an insignificant ooze at the upper angle of a tear or an episiotomy may in a few hours be a large hematoma. Early diagnosis^{8, 9} and evaluation of the case is the next step. Expectant treatment is used when a small hematoma is discovered and does not increase under observation. A hematoma that is enlarging, or a hematoma that is large on discovery, should be incised and evacuated, and the bleeding controlled. This may be accomplished by suture, pressure, pack or hemostatic absorbable gauze, or a combination of these measures. If there has been severe hemorrhage, shock treatment is immediately instituted, blood replacement of course being most important. If infection is present, incision and drainage, culturing and the use of the most specific agent available are advisable. Immediate treatment with streptomycin and penicillin, while culture reports are awaited, seems a sensible plan.

In view of the early ambulation used in hospitals and the shorter hospitalization now popular, more late hematomas may be seen than in the past. The following case is presented with this consideration in mind.

CASE REPORT

A 28-year-old bipara, 7 days post partum, reported to the accident room complaining of severe perineal pain. The discomfort had begun with activity at home after discharge from the hospital. Pain had become so severe that she could not sit comfortably. There had been bright-red vaginal bleeding for 2 days, and the patient had become weak and light-headed. Her obstetrician stated that pregnancy and labor had been normal and that a median episiotomy had been done and a low forceps delivery effected without incident. The usual repair had been made. No lacerations had been observed, and no vulvoperineal mass or discoloration noted. The patient had apparently been in good condition on discharge.

The past history was noncontributory.

Physical examination revealed a hard, symmetrical mass extending about 10 cm above the pubis. The inguinal lymph nodes were enlarged bilaterally, more so on the left. On vaginal examination marked perineal blueness was found, extending beyond the ischial tuberosity left laterally and into the labium, and to the anal margin inferiorly. A gaping episiotomy incision exuded serosanguineous material from two openings, each about 2.5 cm in length. A moderate bloody vaginal discharge was present. Only one finger could be introduced into the vagina with comfort. A mass was found in the left wall about 7 cm inside the outlet, extending superiorly to the fornix and nearly obliterating the vaginal canal.

The temperature was 104.4°F, the pulse 140, and the respirations 22.

The urine showed a trace of albumin. The red-cell count was 2,860,000, with a hemoglobin of 58 per cent, and the white-cell count was not elevated, the blood chemical findings were normal. The blood type was O, and the patient was Rh+.

The diagnoses were late post-partum vulvovaginal hematoma, infected, median episiotomy, infected, and secondary anemia.

General treatment consisted of transfusion, intravenous administration of fluids, penicillin and streptomycin until the culture report revealed colon bacilli, and then streptomycin alone for 4 days.

Local treatment was definitive, incision and drainage of the mass being accomplished under sodium pentothal anesthesia. At this time about 500 cc. of blood clot and dark, thick blood with a strong odor of colon bacilli was evacuated, a culture taken, and the cavity irrigated with physiologic saline solution. The cavity was found to extend to the peritoneal reflection, having dissected superiorly the length of the vagina, to the anal margin inferiorly, to beyond the ischial tuberosity left laterally, and beyond the site of the episiotomy medially. Drains were inserted through a stab wound medial to the left ischial tuberosity and through the wide open episiotomy wound. The cavity was packed through the vaginal incision, and a "T" binder was applied. Packs were changed and drains shortened in 24 hours. All drains and the vaginal sponge were removed on the 6th day. Potassium permanganate douches and sitz baths were then instituted until discharge on the 11th day.

Postoperative examinations revealed excellent general healing and the presence of a painful scar at the site of the episiotomy along with a relaxed vaginal outlet. Excision of the painful cicatrix and perineorrhaphy were accomplished 4 months after the original operation. The patient left the hospital in 8 days. Follow-up examination showed a well healed, firmly supported perineum. The vagina admitted 2 fingers without discomfort. No pelvic abnormality was noted.

SUMMARY

A review of the literature from 1554 to 1948 reveals 188 cases of paravaginal hematoma.

Obstetric hematomas may be immediate or late and are anatomically classed as vulvar, paravaginal, intraligamentary or retroperitoneal, or a combination of these locations.

Early diagnosis and immediate active treatment are advisable because of the high mortality in severe cases.

A case of late post-partum vulvovaginal hematoma, exemplifying many of the points considered, is presented, and its treatment described

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MEDICAL PROGRESS

TUBERCULOSIS

JOSEPH D WASSERSUG, M D *

QUINCY, MASSACHUSETTS

IT IS well nigh impossible for a single reviewer to encompass the entire field of tuberculosis, so vast are its ramifications. In a review such as this, one is forced to limit himself to the highlights of the year, and, even then, some significant contributions may be overlooked or touched upon only lightly.

The fact that tuberculosis mortality continues to show a gratifying decline cannot be overlooked. The death rate for tuberculosis, with few interruptions, has shown a continuous decline since 1910. In 1946, it was only 36.4 per 100,000 population,¹ which amounted to a 9.2 per cent decrease from the rate of 40.1 in 1945. In 1947 the death rate had dropped to 33 per 100,000,² and, according to the Metropolitan Life Insurance Company,³ a record low mortality may have been set in 1948. For their policyholders, the tuberculosis death rate declined from 32.3 per 100,000 in the first half of 1947 to 28.4 in the first six months of 1948, representing a reduction of 12 per cent. On the debit side of the ledger is the fact that in 1947 nearly 50,000 persons in this country still died of tuberculosis, nearly half of them between the ages of fifteen and forty-four. Although the over-all statistics are heartening, the time for complacency is still far off.

STREPTOMYCIN

So much additional evidence has accumulated during the past year for supporting the belief that streptomycin has a favorable influence on the course of tuberculosis as to dispel any doubt about its value. By far the largest series of cases treated with streptomycin is that reviewed by the Veterans Administration and the Army and Navy⁴ and their "current status" report is well worth reading. In summary, it may be said that some degree of benefit may be expected regardless of the site of infection.

*Instructor in medicine Tufts College Medical School, visiting physician in tuberculosis Boston State Hospital outpatient physician Boston City Hospital associate physician Quincy City Hospital chest consultant Harley Hospital

or organs involved. In pulmonary tuberculosis, "streptomycin, in conjunction with bed rest, has been demonstrated to reverse the trend of progressive predominantly exudative moderately and far advanced disease in a formidable majority of cases." In cutaneous sinuses and fistulas, streptomycin has demonstrated a "striking usefulness." Although the end results in tuberculous meningitis and miliary tuberculosis are not quite so good as had been anticipated on the basis of the patients' initial responses, treatment with streptomycin is "mandatory" in these cases. Bone and joint lesions and urogenital lesions show a slow response to streptomycin, and the combination of surgery and antibiotic therapy is indicated in these cases. The results of treatment of lesions of the alimentary tract are "uniformly and remarkably favorable." For all forms of tuberculous peritonitis, streptomycin is regarded as an effective remedy. Since the drug brings about improvement in 80 to 90 per cent of cases of tracheobronchial and laryngeal tuberculosis, it should be considered as a prime form of therapy in such patients.

Aside from these generalities, probably the most notable advance clinically is the demonstration that the relatively high doses of streptomycin previously employed can be reduced to lower, less toxic, levels without any appreciable impairment in effectiveness. Along with this, there has been a gradual reduction in the cost of the drug so that it is now more readily available to noninstitutionalized as well as institutionalized patients. An amount of 1 gm daily in two divided doses at twelve-hour intervals for a period of one hundred and twenty days appears to be adequate, and 0.5 gm daily for as short a period as forty-two days may prove to be effective in some cases. If the latter scheme proves successful, toxic reactions from streptomycin may be reduced to the vanishing point.

When the therapeutic possibilities of streptomycin were first being explored it was wisely decided that additional measures other than bed rest had best be withheld so that any decision about the effectiveness of the drug would not be beclouded by other factors. Since streptomycin has already proved its effectiveness, this phase of evaluation can be said to be completed, and the time has now come when strict scientific evaluation is of less concern than the necessity of providing the patient with every form of treatment that will rid him of bacilli and restore him to health as quickly as possible. One may thus see streptomycin being given simultaneously with usual collapse treatments and, although such varied forms of therapy may be difficult to evaluate from the scientific standpoint, there is reasonable likelihood that the period of the patient's disability will be reduced. Streptomycin therapy is rarely definitive in the sense that it often does not produce complete clearing of the tuberculous lesions and that a considerable percentage of relapses occur. "Its most frequent usefulness appears, therefore," comments the committee,⁴ "to lie in conjunction with collapse therapy." The judicious use of streptomycin often makes collapse therapy a possibility in cases in which collapse would heretofore have been impossible or unlikely for one reason or another. According to the committee, the optimum time to induce collapse is during the first weeks of streptomycin therapy before resistance develops in the bacilli. From a practical standpoint, any patient with tuberculosis should receive any and all therapeutic measures, antibiotic and collapse, after a short period of observation has demonstrated their need.

Since the toxicity of streptomycin has been significantly reduced through the simple expedient of lowering of the average daily dose, only one significant drawback remains to its greater effectiveness. That drawback is the development of resistance (or, better, loss of sensitivity) of tubercle bacilli to the drug in some patients under treatment. Development of resistance is perhaps the chief reason for *not* using streptomycin in minimal lesions. In such cases the antibiotic is generally withheld since the prognosis is usually favorable without it, and, besides, should treatment with streptomycin become necessary at a later date, the drug would prove ineffective if loss of sensitivity had taken place. The increased resistance to streptomycin can be considerable and may be as high as a thousand times or higher. As a matter of fact, a curious paradox has recently been reported in the recovery from a patient of a strain of tubercle bacilli whose growth was considerably *enhanced* by the presence of streptomycin in the culture medium. The patient from whom this organism was isolated had been receiving the drug for ninety-six days for a pulmonary infection. In some cultures it was found that growth occurred in the presence of as

much as 100 microgm, whereas no growth was evident on the medium without streptomycin.⁵

The development of a loss of sensitivity of the tubercle bacillus during streptomycin therapy has recently been studied in a joint program of the Yale University School of Medicine and the Laurel Heights Sanatorium under the auspices of the American Trudeau Society.⁶ These studies are worth noting, for they are fairly typical of the universal experience in the development of resistance. A group of 16 patients with pulmonary tuberculosis were treated with 16 gm of streptomycin in six divided doses for a period of four months. Sputums or gastric washings were collected at routine intervals, and tubercle bacilli were isolated by culture from these specimens. After growth had been obtained, transfer of part of a suitable colony was made to a tube of modified Dubos-Davis medium for *in vitro* sensitivity tests. It was found that in all 16 cases, the strains of the bacilli isolated prior to treatment were highly sensitive to streptomycin. Loss of sensitivity (tenfold increase in resistance) began to appear by the end of the first month of therapy, together with conversion of positive sputum or gastric washings to negative in other cases as determined by culture. By the end of the third or fourth month of therapy, cultures were positive in only 9 of the 16 cases. Sensitivity tests of the organisms from these positive cultures indicated that all the organisms had developed a tenfold or greater increase in resistance. Five of these nine strains developed a tenfold to fiftyfold increase in resistance, in the remaining four strains the increase was a hundred to greater than two thousand times.

How streptomycin resistance can be a cause of therapeutic failure is graphically illustrated by a case of miliary tuberculosis reported by Muschenheim, McDermott and Bunn.⁷ The patient was a twenty-one-year-old man whose miliary tuberculosis was associated with cervical and mediastinal lymphadenitis of an extreme degree. Tubercle bacilli isolated from this patient were initially sensitive to less than 1 microgm of streptomycin per cubic centimeter of medium *in vitro*. With the institution of streptomycin therapy (30 gm daily), fever subsided, the superficial lymph nodes began to shrink visibly, stupor disappeared, the appetite became normal, and a rapid gain in weight ensued. For five weeks the patient seemed to be in complete remission. At that time, resistance of the organisms to streptomycin developed so that all the original symptoms returned with increased severity, and cultures of the tubercle bacilli revealed that the organism was now resistant to concentrations of streptomycin in excess of 1000 microgm per cubic centimeter. The temperature became elevated, the downhill course was progressive, and death ensued seven weeks after the clinical onset of the relapse and five months after the institution of treatment.

Considerations of this type temper one's enthusiasm for the drug and certainly provide good reasons for not using it in the early, minimal case of uncomplicated pulmonary tuberculosis whose prognosis is usually favorable on bed rest or collapse therapy. This experience further indicates that the action of streptomycin is still to be regarded as *suppressive* rather than *curative*.

Since streptomycin is far from an ideal therapeutic agent, some efforts are being made to use other therapeutic substances along with streptomycin for possible synergistic effect. One such agent being explored is para-aminosalicylic acid (PAS). Youmans and his co-workers⁸ have found evidence that such a synergism between streptomycin and PAS exists in mice, although it was possible to recover viable tubercle bacilli from all the mice treated regardless of the intensity of the therapeutic schedule. They note further "Since the usefulness of para-aminosalicylic acid for the treatment of clinical tuberculosis is not known, the importance of these results in relation to the treatment of clinical tuberculosis can only be a subject for speculation." McClosky, Smith and Frias,⁹ on the other hand, have carried out extensive researches on the toxicity, fate in the body and therapeutic efficacy of PAS in rabbits and guinea pigs. In these animals PAS had but little therapeutic effect by itself, and, when combined with streptomycin, it showed no more than a summation of effects without any indication of potentiation. In the light of these experiments, the value of PAS for human beings is doubtful.

Better results both experimentally and therapeutically have been obtained when streptomycin is combined with a sulfone such as promin or promizole. According to some investigators,¹⁰ promizole can be given for a period of years without any apparent major toxic effects. Promizole seems to have an inhibitory action on hematogenous tuberculosis although clinical evidence of its action is usually delayed until at least six weeks after the drug is first given. According to this concept, if streptomycin and promizole are given together, a prompt action is obtained from the streptomycin and a more delayed effect is obtained from the promizole. Considerations of this nature prompted Lincoln, Kirmse and DeVito¹⁰ to give this combination of drugs to 7 patients suffering from tuberculous meningitis. Promizole was administered orally in a total daily dosage of 0.5 to 1.0 gm, and this dose was gradually increased until a blood level of 2 to 3 mg per 100 cc was obtained. The streptomycin was given in doses of 0.5 to 2.0 gm intramuscularly, and, besides, all patients received 0.1 gm intrathecally daily at least during the first week of treatment. On this plan of management 6 of the patients survived and were apparently well three to eight months after institution of treatment. This is a remarkably good record for a disease as

terrible as tuberculous meningitis, although the authors are well aware of the fact that their patients have not been under observation for a sufficiently long period to be considered "cured."

Deserving of some mention is the report by Slotkin¹¹ in which streptomycin therapy is combined with injections of an ethyl ester of chaulmoogra oil. This author believes that the fatty capsule of the tubercle bacillus can be dissolved by the chaulmoogra esters, and thus the organism may be rendered more susceptible to the action of the antibiotic. A brief experimental and clinical experience on urogenital tuberculosis is cited in the preliminary report, but many more data are necessary before this form of therapy can be extended more widely into clinical practice. One direction that experimental investigation might take is suggested by the studies of Karlson and Feldman¹² on the subeffective dose of streptomycin in experimental tuberculosis in guinea pigs. These investigators wisely point out that in a study of the effect of two or more chemotherapeutic agents on an experimental infection, it is necessary that the dose of each drug be low enough so that one of the drugs alone will not be responsible for the total therapeutic response. As far as guinea pigs are concerned, their results indicate that if the daily dose of streptomycin is kept at 20 mg, it may be considered as being subeffective and suitable for testing the additive or synergistic action of other compounds.

PNEUMOPERITONEUM

During the past few years pneumoperitoneum has definitely emerged as a valuable form of collapse therapy on a par with pneumothorax if not actually surpassing it in many cases. Banyai,¹³ one of the pioneers to use this form of treatment as far back as 1931, has recorded his experiences and that of others in considerable detail. Mitchell and his colleagues,¹⁴ in North Carolina, have summarized the literature since 1937 in convenient tabular form and have described their own experience with this procedure, which covers 703 patients, 474 of whom were treated for three months or longer. Although they do not regard their results as offering "final proof of the efficacy and safety of pneumoperitoneum," they believe that pneumoperitoneum may be preferable to conventional collapse therapy or simple bed rest in cases with fairly extensive, predominantly productive disease with positive sputum provided the cavities are not too old or thick walled. If pneumoperitoneum is used in conjunction with phrenic paralysis, it is best to start pneumoperitoneum prior to surgery because with it one gains valuable information about the mobility of the diaphragm and its attainable elevation. In their own experience, Mitchell et al.¹⁴ found that the use of pneumoperitoneum for an average of fifty-four and a half weeks was responsible for 57 per cent satisfactory

results in 188 white patients and in 37 per cent of 286 Negroes, all of whom were "not amenable to conventional forms of collapse therapy"

Since pneumoperitoneum is a relatively new procedure exact definition of its indications and contraindications is lacking. According to Aronovitch, Caswell and Zadé,¹⁶ the indications for pneumoperitoneum may be summarized as follows: moderately advanced bilateral tuberculosis when artificial pneumothorax cannot be given, unilateral disease in which pneumothorax is impossible for one reason or another, to supplement phrenic crush, as an adjunct to artificial pneumothorax, as a preliminary measure in early bilateral cases, and for basal lesions with or without cavitation. Of 42 cases (1800 refills) carried out by this group, improvement was noted in 24, or 57 per cent, and there were no major complications.

Pneumoperitoneum has many advantages over conventional pneumothorax, some of which are listed by Anderson.¹⁶ Pneumoperitoneum does not interfere with the normal physiology of the intrapleural space in the way that pneumothorax does, and it does not create thickening of the pleura or produce an unexpandable lung. In bilateral disease, pneumoperitoneum has the advantage that both lungs can be collapsed by one injection of air. A further advantage is that the underlying lung can be visualized while treatment is continuing, and progress can be followed better than with pneumothorax. Pneumoperitoneum is a reversible procedure—one that can be induced, discontinued and reinduced almost at will. Spontaneous pneumothorax and bronchopleural fistulas are avoided. Anderson¹⁶ states:

Perhaps the outstanding advantage of artificial pneumoperitoneum over artificial pneumothorax, as far as the general practitioner is concerned, is the fact that fluoroscopic control is not essential. The operator simply injects enough air to inflate the abdomen snugly. He need not worry whether he is puncturing the lung, collapsing it too far, or losing the space—any of which complications may occur with artificial pneumothorax.

Fluoroscopic guidance is always valuable, however, even though it may not be essential in every case. Further experience will, of course, be necessary to determine whether pneumoperitoneum is preferable to pneumothorax in the outpatient or ambulatory management of tuberculous patients.

Complications with pneumoperitoneum are less frequent than with pneumothorax, but complications may occur. Air embolism is a possibility,¹⁷ and death from this complication has been noted.¹⁸ Sterile peritoneal effusions occur in about 8 per cent of the cases, and although they may require paracentesis, they do not necessarily indicate the abandonment of the pneumoperitoneum. On the other hand, peritonitis, either tuberculous or pyogenic, may be a serious complication and may necessitate discontinuation of pneumoperitoneum and the institution of suitable chemotherapy or

antibiotic therapy. Peritoneal adhesions may be seen in a great number of cases roentgenologically, but they seldom cause trouble. Penetration of abdominal viscera is a complication that is dreaded by beginners but is one that seldom occurs. Subcutaneous emphysema is a readily avoidable complication.

Although the technic of inducing and maintaining pneumoperitoneum varies somewhat from operator to operator, it is admittedly more simple than pneumothorax. Induction is usually carried out in the left lower quadrant under local procaine anesthesia, and the details can be found in any of the recent articles cited above. The amount of air given at the initial injection varies from 400 to 800 cc and refills, at intervals of seven to fourteen days, amount to anything from 500 to 1500 cc or more. Positive pressures are used, and the final pressure is kept under 20 mm of water, the average being 12 to 16 mm. There is no fixed rule in this respect, and individual variability must be taken into consideration. Manometric readings in pneumoperitoneum do not have the precise significance that they have in pneumothorax.

Although thousands of patients have been treated by pneumoperitoneum most of them have received treatment within the past few years, and suitably long follow-up material is not available. Trimble et al.¹⁹ have studied quite carefully 407 consecutive cases, of which 382 were adequately followed. In this latter group arrest of the disease was possible in 57 per cent, and an additional 13 per cent were definitely improved. It is to be noted that in their patients, arrest was achieved in 82 per cent of the minimal cases, in 79 per cent of those that were moderately advanced, and in 39 per cent of the far-advanced cases. Of 233 patients with cavitation, 47 per cent became arrested, and another 18 per cent were definitely improved. These results are at least as good as, if not better than, those in any comparable series treated by pneumothorax.

A recent editorial by Howlett²⁰ presents a sound appraisal of the present status of pneumoperitoneum without any bias or prejudice. He points out that there is still great divergence of opinion regarding the indications, effectiveness and usefulness of pneumoperitoneum in spite of the fact that it has been used for more than a decade. At present, he says, pneumoperitoneum seems to be heading for its phase of rapid expansion as a form of treatment, and, without doubt, some disillusionment with it will develop, especially when it comes to be used in forms of the disease in which it is not effective. Furthermore, as pneumoperitoneum ascends in vogue, it will be employed by more and more operators who are not adequately trained either in its administration or in the evaluation of the cases in which it may not be indicated. On the other hand, Howlett admits that he knows of no case "in which a physician has used pneumoperitoneum adequately

on enough patients for a sufficient period of time and has then discarded it as a procedure of no value." The chief danger of pneumoperitoneum, he believes, is not the procedure itself but the ease with which it may be given and the fact that the readiness with which it is tolerated by most patients may lead to its indiscriminate and excessive use. Howlett's editorial should be read by everyone attempting to perform pneumoperitoneum, especially the beginner.

Sporadic reports have appeared about the possible usefulness of pneumoperitoneum in the treatment of bronchial asthma. Attention is again called by Rubin and Gass²¹ to a case of intractable asthma that responded to this form of therapy. It is interesting to note that in the reproductions of the roentgenograms that accompany the article, considerable basal emphysema is present and that the amount of pneumoperitoneum used seems to be less than is customarily employed in the treatment of tuberculosis. Further investigation on the use of pneumoperitoneum in such cases is definitely indicated.

BCG

Evidence continues to accumulate that BCG (*Bacillus Calmette-Guérin*) is a safe and relatively efficacious vaccine for the control of tuberculosis. The policy of the American Trudeau Society²² regarding its use can be briefly summarized as follows: the degree of protection afforded by BCG is neither complete, nor is the duration of the induced immunity permanent or predictable. Nevertheless, it is recommended that the immunization be made available to medical and hospital personnel who are exposed to infectious tuberculosis, persons who are unavoidably exposed to infection in the home, inmates and employees of various institutions such as mental hospitals and prisons, and others who are considered to have a low resistance to tuberculosis and who live in communities in which the tuberculosis mortality is high. Vaccination of the general population is not recommended at present except under certain carefully controlled conditions. It is also not recommended that the vaccine be made available for general distribution since there is still some uncertainty about the most effective strain of BCG to be used and the most effective method of vaccination. It is the belief of the American Trudeau Society that the most effective methods of controlling tuberculosis are those already established, such as more intensive case-finding, segregation, intensive therapy and rehabilitation. BCG is not a substitute for approved hygienic procedures. A similar opinion regarding BCG is held by the United States Public Health Service^{23, 24}. It is perhaps unnecessary to add that BCG should only be given to persons who are negative reactors to tuberculin.

It is interesting to compare the limited experience with BCG in this country with that obtained elsewhere. In Scandinavia²⁵ vaccination with BCG has been established as a public-health measure since 1926, although it is by no means the only antituberculosis weapon employed. Other measures, such as tuberculin surveys and x-ray examinations, are intensively conducted, and, with such a vigorous program, the tuberculosis mortality in these countries has been reduced from 250 per 100,000 population in 1900 to less than 70 in 1944. So favorable were the early results with BCG that a national BCG laboratory was established in Norway in 1936, and, subsequently, BCG vaccination became obligatory for all tuberculin-negative student nurses. With the cruel German occupation of Norway in 1939, large numbers of tuberculin-negative young people were crowded into small and unhygienic quarters, and epidemics of tuberculosis were reported in all parts of the country. Political interference forced BCG vaccinations to be given surreptitiously, and yet, in spite of all these difficulties, the statistics at the end of this unhappy period indicated a "very considerable immunizing efficiency of the vaccine."

In Sweden, all medical students and pupil nurses are now tested before beginning hospital service, and the nonreactors are vaccinated²⁶. Conscripts in the services are vaccinated at the beginning of their term of service, and so are the majority of school children in the last class of primary school. In the city of Örebro the whole population has been tested, and the nonreactors have been vaccinated with BCG. All newborn babies are also vaccinated. On the basis of this experience, Malmros²⁶ urges BCG vaccination as a part of any modern tuberculosis program. He further advises that all vaccinated persons be checked at stated intervals and that those who have become tuberculin negative be revaccinated.

In this country, the most extensive experience with BCG is that reported by Aronson,^{27, 28} of the Office of Indian Affairs, and by Rosenthal and his colleagues²⁹ at the Municipal Tuberculosis Sanatorium in Chicago. Some of the statistics of the former investigator have been previously reviewed³⁰. The latter group has performed extensive laboratory investigations on BCG and conducted a study of the effects of vaccination on the following six groups of patients: newborn infants at the Cook County Hospital, medical students at the University of Illinois, infants born of tuberculous parents anywhere in Chicago, student nurses at the Cook County Hospital, children at a federal housing project, and inmates of a mental institution. Their studies, which have been in continuous operation for thirteen years, constitute the longest continuous experiment on BCG vaccination in the United States.

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In this country, the most extensive experience with BCG is that reported by Aronson,^{27, 28} of the Office of Indian Affairs, and by Rosenthal and his colleagues²⁹ at the Municipal Tuberculosis Sanatorium in Chicago. Some of the statistics of the former investigator have been previously reviewed.³⁰ The latter group has performed extensive laboratory investigations on BCG and conducted a study of the effects of vaccination on the following six groups of patients: newborn infants at the Cook County Hospital, medical students at the University of Illinois, infants born of tuberculous parents anywhere in Chicago, student nurses at the Cook County Hospital, children at a federal housing project, and inmates of a mental institution. Their studies, which have been in continuous operation for thirteen years, constitute the longest continuous experiment on BCG vaccination in the United States.

It can be said that these clinical experiments have proved reasonably successful. Of 2831 newborn

infants who were not in household contact with tuberculosis, there were 11 cases of tuberculosis in the vaccinated as against 39 in the controls. One death was recorded in the vaccinated, and 7 in the controls. In 1159 siblings the tuberculosis rate per thousand was five times as great in the controls as in the vaccinated. Among 256 newborn infants, when tuberculosis was present in the household and when isolation in foster homes was practiced in the controls and in the vaccinated alike, there were 2 cases of tuberculosis in the vaccinated as compared with 5 in the controls. In the federal housing project 699 children were vaccinated, 625 controls did not react to tuberculin, and 275 reacted to tuberculin and were not vaccinated. Considering the negative and positive reactors not vaccinated, there were 7 cases of tuberculosis, of which 2 were fatal, against no cases of tuberculosis in the vaccinated group. It was found that subsequent to vaccination a positive tuberculin test persisted as long as six years in the great majority of the children. Additional studies by Neiman and Loewinson³¹ have suggested that BCG inhibits the development of primary as well as secondary tuberculosis in infants. Their investigation, which is based on a study of 13,470 chest roentgenograms, furnishes additional proof of the efficacy of BCG.

Since successful vaccination with BCG converts a negative reactor to positivity, the vaccine should not be used in areas where tuberculosis mortality and morbidity are low and where tuberculin negativity is prevalent. The chief exponent of this viewpoint is Myers,³² who has repeatedly pointed to the admirable accomplishments in Minnesota, where tuberculosis has been largely eradicated. This has been achieved without the use of vaccination and through rigid adherence to sound public-health principles. To quote from Myers:

The tuberculin test is our only refined epidemiological agent. Indeed, it is only through its continued use that total eradication can be achieved. So-called immunizing substances, such as BCG and the vole tubercle bacillus, which sensitizes the tissues to tuberculoprotein, could serve no purpose except as a smoke screen for the tubercle bacillus in Minnesota. If used, they would nullify our most effective weapon—the tuberculin test. Moreover, their efficacy even in tuberculosis control has never been proved in any sense of the word. They remain in the same position as their dozens of predecessors, namely, the theoretical and experimental stage. In parts of the world where BCG has been used, no achievement in tuberculosis control has been reported that even remotely approaches that in the United States, where sound epidemiological methods have been in vogue.

It is obvious, however, to the critical student of the subject that the situation in the United States, where “sound epidemiological methods” have been allowed to flourish unhampered by war, is entirely different from that in the devastated nations of Europe or some of the backward countries of South America. Even in the United States the situation in Minnesota may be likened to a safety zone that lies in the midst of streaming traffic. To carry the

analogy a bit farther, the wise Minnesotan will remain on his little island if he wishes to retain his health. To travel abroad without any immunity might prove particularly hazardous. Of course, if he so desired, he might remain where he is until traffic around him quieted down, but that might take a good many more years. In brief, Myers's argument applies very well at the present time to Minnesota. It does not, as yet, apply to the rest of humanity.

BACTERIOLOGIC CONSIDERATIONS

Although there has been a constant interest in the discovery of improved methods for culturing tubercle bacilli, there is no doubt that this interest was given considerable impetus by the reports of Dubos³³ and Dubos and Davis³⁴ on the use of liquid mediums for the rapid and submerged growth of these organisms. So reliable are the cultural methods at the present time that they have to a large extent replaced the more costly animal tests. Cultural methods have the additional advantage that they are superior in disclosing not only small numbers of virulent mammalian bacilli but also tubercle bacilli of low or moderate virulence. According to Corper and Bain,³⁵ the chief advantage of the animal test is that it overcomes the problem of eliminating the undesirable contaminating organisms without injury to the virulent tubercle bacilli. They have found, however, that by the use of trisodium phosphate in the culture medium, this disadvantage of the culture method is largely overcome.

The Dubos medium is being used widely for the culture of material obtained directly from the patient for the identification of tubercle bacilli. Goldie³⁶ reports that of 400 sputums examined by this method 34 were positive by culture and negative by smear. He states that compared with other culture methods, “the use of the Dubos medium is inexpensive, easily learned by an average technician, suitable for daily examinations of a large number of specimens, and, what is more, offers the advantage of a rapid (within 8 to 15 days) culture diagnosis of sputa containing relatively small numbers of *M. tuberculosis*.” Folev³⁷ has studied 197 specimens obtained from various sources by both culture and inoculation methods. He believes that the method is valuable but points out that saprophytic mycobacteria from urine and gastric contents as yet cannot be sufficiently differentiated from tubercle bacilli for the exclusive use of these mediums for the specific diagnosis of tuberculosis. In these cases animal inoculation studies must be done for positive identification of the organism.

Cultural methods are of value not only in detecting tubercle bacilli but also in testing various antibiotic and chemotherapeutic agents. Although many such reports have appeared in the literature in the past year, only one is cited here as being illustrative of its value. Wong et al.³⁸ have noted

that the earlier attempts to demonstrate any antibiotic activity of subtilin *in vitro* by use of Long's synthetic medium have ended in inconclusive results. They therefore tested subtilin against a suitable strain of human virulent tubercle bacilli in Dubos medium and found that under the conditions of the test a 1:400,000 dilution of subtilin regularly inhibited the growth of these organisms and that dilutions of 1:20,000 were bactericidal. Rapid testing of new antituberculosis substances can thus be achieved through the use of the Dubos medium. The simple medium of human blood and glycerin, described by Dunphy and Fousek,³⁹ may also prove valuable in this direction.

Arguments have appeared from time to time supporting the use of alcohol as a disinfectant for both tubercle bacilli and other micro-organisms. The latest contribution to this argument is that presented by Smith,⁴⁰ and it is worth the attention both of private practitioners who have occasion to deal with tuberculosis and of hospital administrators. Smith cites extensive literature of this subject and his own many experiments. He finds alcohol to be an effective disinfectant against tubercle bacilli if attention is paid to the type of contamination and the concentration of the alcohol employed.

SURGICAL CONSIDERATIONS

In recent years the indications for pulmonary resection have come to be clarified and the procedure standardized in much the same way as thoracoplasty. According to Moore⁴¹ the indications for resection of tuberculous lungs include thoracoplasty failure, basal disease that fails to respond to conservative measures, endobronchial disease associated with tension cavities or pulmonary suppuration, tuberculoma and the so-called "destroyed lung" with extensive caseation and cavitation. Moore believes that the contralateral lung should be comparatively free from disease, or that any existing focus should be relatively stable or arrested. He further states that he can see "no sensible reason why the operation should be attempted in patients who have had bilateral disease and whose vital capacity is so low that pulmonary resection leaves them hopeless cripples, even though it may convert their sputum to negative."

At present, as Clagett and Seybold⁴² point out, the greatest hazard to patients with tuberculosis undergoing resection is late spread of the disease. This problem of late spread or reactivation has plagued every thoracic surgeon, and, in every case, statistical surveys of late results are found to be definitely inferior to the immediate mortality or morbidity. This is understandable for two reasons: tuberculosis is a generalized disease, and the removal of the most obvious focus does not rid the patient of his infection or alter his immunologic reaction to the tubercle bacillus, microscopic amounts of "spilling" during the operation into the un-

resected lung may not be immediately noticeable, and yet the organisms have been "planted" only to make their visible appearance at a later date.

The limited and restricted role that resection must play in the treatment of tuberculosis is brought out in the figures cited by Clagett and Seybold.⁴² Of 29 patients operated upon in their series (14 cases of lobectomy and 15 of pneumonectomy) 19 were clinically well and had sputum free of tubercle bacilli. Four patients were dead, 5 had active disease, and 1 was untraced. Sweet⁴³ also finds that the late results of resection are inferior to the immediate results and urges that at least one year be allowed to elapse before any report is made regarding such surgical procedures. He notes that of the 6 cases of lobectomy reported by Churchill and Klopstock in 1943, only 4 can be said to have done well three years later, and 3 of these 4 would probably have done equally well under thoracoplasty. "What appear to be very encouraging results at first," says Sweet, "have many times turned out to be disappointing when appraised some months later." He points out that of 13 reactivations following lobectomy (in a total of 27 cases), 11 occurred as a late complication. Of 10 reactivations after pneumonectomy (in a total of 36 cases), 7 were of late occurrence. It is important to note that Sweet's study includes only patients operated upon prior to the advent of streptomycin. It seems likely that streptomycin will minimize these complications, but it should also decrease the necessity for such radical surgery.

Perhaps the most enthusiastic proponents of lobectomy and pneumonectomy as a surgical treatment of tuberculosis have been Overholt and his group.⁴⁴ They believe that many of the patients for whom these procedures have been performed are "desperate-risk" patients whose death might otherwise have been anticipated with great certainty. "We feel," they say, "that *any salvage in this group of patients, regardless of how small, can be considered pure gain*." Their analysis of 88 patients treated by 92 resections and followed from two to twelve years shows that 68 patients could be considered as reasonable risks and 24 were desperate risks. Among 58 patients treated by pneumonectomy, there were 13 deaths in the sixty-day postoperative period and 11 late deaths, making a total case fatality of 41 per cent. Among 33 patients treated by lobectomy, there were 3 postoperative deaths and 3 late deaths. Only 14 of the 33 were clinically well and had consistently negative sputum. It must be noted that these statistics, too, antedate the use of streptomycin.

That streptomycin is a drug of much benefit in the management of surgical patients is already borne out by experience. What effect the drug will have on the incidence of late spreads, however, is still not known. Glover et al.⁴⁵ have cited their experience with streptomycin in conjunction with resection,

and their results, to date at least, are encouraging. They suggest that prophylaxis against immediate spread may be obtained and some other surgical complications may be reduced by streptomycin, and the doses needed to accomplish this may be smaller than those generally required for therapy. They believe that if the surgical mortality can be further reduced by a decrease of such complications, the indications for radical surgical treatment will be broadened. It seems to me, however, that although the *indications* may be broadened by the use of streptomycin, the over-all necessity for radical surgery may be reduced.

It may be well in this discussion of surgery to call attention to two procedures or technics that may prove of value in certain cases. The first is decortication of the lung in organizing hemothorax and empyema. In these cases the lung is bound down by a thick shell of fibrinous membrane that severely restricts respiratory activity. In certain cases it is possible to peel this membrane off, and one can then actually see the lung re-expand to fill completely the thoracic cavity. Lowe⁴⁶ reports 3 cases in which the decortication procedure was performed, in 1 of which the patient had tuberculous pleurisy and atelectasis. The postoperative course was excellent, and the patient gained weight and was relieved of his respiratory disability.

The second technic worth mentioning is the use of lucite spheres that are inserted into the thorax to assist in collapsing the lung in some cases of extrapleural pneumonolysis. Cases chosen for this procedure are those that would ordinarily be considered candidates for thoracoplasty, but the procedure has the advantage of less chest deformity. Although the indications for this operation are reasonably well established, it should be pointed out that there is only one year's experience and 30 operated cases behind this method and that it would be well to follow these patients for a longer period before the exact role of lucite plombage in the treatment of pulmonary tuberculosis can be evaluated. The authors⁴⁷ are themselves cognizant of this fact and make note of it in their paper.

REHABILITATION AND PSYCHIATRIC ASPECTS

It is safe to say that there has been more nonsense written about rehabilitation as it pertains to tuberculosis and about the mental attitude of tuberculous patients than there has been on any other phase of this complicated disease. Some of this stems from the fact that each specialist, be it social worker, rehabilitation expert or epidemiologist, is so concerned with his small specialty that he fails to see the forest because of his emphasis on an individual tree. Clinicians, too, have been accused of looking too closely at the patient's lungs to the exclusion of the body and soul in which the lungs are but a small part. Nevertheless, it does not follow, as some have suggested,⁴⁸ that the

clinician has to be "assisted by medical social workers, institutional and public health nurses, occupational therapists, and librarians" to realize the total portrait of the drives and dreams of the men and women who submit themselves to his care. Any good doctor does all that in his daily handling of his patients.

Pinner⁴⁹ points out that reports on the final results of rehabilitation are still too few to be significant. He states

That rehabilitation work is a necessary and important part of the successful treatment of many patients is quite generally accepted, it has come into its own during the last quarter of a century, in word and program, if not in action and reported results. If advocates of any medical or surgical treatment of tuberculosis had, for twenty or even ten years, written profusely on plans, methods, set-ups, theory and — the philosophy (a beloved misnomer!) — of some treatment without publishing statistically acceptable reports of results in terms of numerically significant case reports, they would, by now, find their treatment pretty well discredited. But this is, in essence, the present status of rehabilitation work.

For those who are interested in detailed discussions on the psychiatric appraisal of the tuberculous person, two recent articles^{50, 51} may prove helpful. The impression that one gains from these articles, however, is that the tuberculous patient is an exceedingly complicated person, buffeted by the storms of his emotions and anxieties. The implication is that many tuberculous patients should have the benefit of a psychiatrist in their routine management. As a matter of fact, another author⁵² states

There is a real challenge to psychiatry in the coming years to contribute materially to the improvement of the tuberculous. To do this, there must be close co-ordination of effort between individuals and agencies dealing with tuberculosis and mental hygiene. With the appearance of national interest in the mental hygiene movement, and its sponsoring through federal and state appropriations, the means are now available for the formation of a unified program of medical, psychiatric and sociologic treatment of the patient with tuberculosis.

Yet, it seems to me, the problem is far less involved. After all, as Dufault⁵³ points out, the personality of the tuberculous patient is, on the whole, uncomplicated.

He has his whims, his quirks, his idiosyncrasies, no doubt, but they run along the lines of yours and mine. He knows anger and resentment — and who does not? — but he is familiar with appreciation and gratitude. He can laugh or cry, smile or frown, talk or sulk, according to his moods. These are normal behavior traits which sound their harmonious or discordant notes in the shop and in the office as well as in the sanatorium.

It is well to note that this evaluation comes from one who has spent many years in the study of tuberculous patients and is not based on an "interview" that lasts an hour or two.

Perhaps the best of the recent discussions that deal with the psychology of the tuberculous patient is that by Moorman.⁵⁴ His experience in the treatment of the tuberculous has also extended over a great many years. Moorman believes that on a

broad psychosomatic basis every patient with tuberculosis is sick in mind as well as in body. That does not mean, however, that every victim of the disease needs the attention of a psychiatrist. "With rare exceptions," says Moorman, "the tuberculous patient needs only a wise phthisiotherapist who knows that mind and body are so interdependent that there can be no life when they cease to function as one." He adds that under ordinary circumstances the patient's interest should not be divided between several doctors, and his confidence in his attending physician should not be disturbed. On the average, the suggestion that a psychiatrist should be called to assist in the management of the case would only serve to spotlight the patient's mental aberrations "and aggravate his psychic conflict which otherwise might have resolved in the course of time almost, if not quite, unconsciously."

Since there is often a relation between the patient's mental state and the problem of irregular discharge from the sanatorium, the exhaustive study of such discharges by Tollen⁵⁵ is worth particular mention. Although his analysis of the situation is based on the experience of the Veterans Administration, the conclusions that he reaches have much wider applicability. It is apparent that a great deal of the responsibility of irregular discharges lies with the first physician who "breaks the news" to the patient that he has tuberculosis. The understanding and the reassurance that the patient receives from his doctor are far more important in creating a frame of mind conducive to successful hospitalization than any help the patient receives from others. In other cases, inadequate personal attention by the physician at the sanatorium is cited as a cause of premature departure of the patient from the hospital. Among the many suggestions that are made for correcting some of the evils that now exist, an excellent one is redefinition of the term "against medical advice." It is pointed out that if the staff doctor *knows* that a particular veteran requesting discharge will receive proper care at home and if no local health ordinance is violated, it should be unnecessary to discharge a patient "against advice" even though he still requires positive treatment for tuberculosis. Many other valuable suggestions are advanced by Tollen, and his article should be read by all sanatorium directors and their professional subordinates.

1159 Hancock Street

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 35121

PRESENTATION OF CASE

First admission A thirty-two-year-old woman entered the hospital for treatment of an old knee injury sustained two and a half years previously, when she severely bumped and twisted the left knee in a fall from a stepladder.

The initial pain and swelling subsided within a few weeks, and she was able to walk about fairly well despite some aching pain, stiffness and slight weakness, which persisted for about one year. Nine months before entry she again severely wrenched the left knee while running and subsequently suffered pain and stiffness on walking. Occasionally the knee gave way under her, although it never really locked. She consulted a doctor, who noted bulging and tenderness of the medial side of the left knee joint. X-ray films were reported as normal. An operation was performed, with removal of a torn medial meniscus. Following operation the knee continued to be painful, and she was unable to extend it completely, despite physiotherapy. Approximately five months later the knee was re-explored, and a loose body removed. This failed to bring any improvement, and the stiffness, failure of extension and aching pain continued.

The past history was noncontributory except for congenital syphilis manifested by interstitial keratitis of the right eye, which was intensively treated by arsenicals, bismuth and penicillin. The blood Wassermann reaction continued to be positive despite therapy.

Physical examination showed a well developed and well nourished woman. There was interstitial keratitis of the right eye, but the pupils reacted to light and accommodation. The left knee was held in 20° permanent flexion, with a flexion swing of 60°. There was considerable tenderness on palpation of the joint, most marked laterally.

The temperature was 98°F, the pulse 70, and the respirations 20. The blood pressure was 135 systolic, 80 diastolic.

Examination of the blood disclosed a white-cell count of 8100, with 81 per cent neutrophils. Both the blood Wassermann and Hinton tests were positive. X-ray films of the left knee showed that the joint surface was smooth, but the space was narrowed, and there was marked thickening of the soft tissues of the joint space. There was no bone destruction (Fig 1 and 2). The right knee showed no definite abnormality. A tuberculin test in a dilution of 1:100,000 was negative.

The knee was manipulated under anesthesia and brought to as much extension as possible, but there remained 20 to 25° fixed flexion. Following this the temperature spiked daily to 100 and 101°F for about five days. She then became afebrile and on exercise function improved considerably so that she was able to flex the knee 80° and lacked only 5° of full extension.

Second admission (two months later) Following discharge the patient was able to walk with crutches and to continue her exercises. She still had diffuse soreness on walking and at times suffered from a burning pain over the medial aspect of the joint, even at rest. Use of the knee definitely aggravated the pain and swelling of the knee.

Physical examination was unchanged except for considerable increase in the swelling and thickness of the periarticular tissues of the left knee posteriorly as well as to each side. There was diffuse tenderness and increased warmth.

Laboratory studies showed normal urine and blood counts. The sedimentation rate was 36 mm in one hour.

On the second hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. WILLIAM S. CLARK: This record represents a common problem in the differential diagnosis of

monoarticular joint disease. The basic phenomenon responsible for the symptoms and signs described here may range all the way from reversible, poorly understood inflammatory processes of the synovial tissues to highly malignant and rapidly fatal tumors. Adequate clinical information and sound clinical hypothesis are particularly important because it is sometimes difficult to obtain adequate tissue for examination from various joints for anatomic reasons. We assume that in taking this history particular attention was paid to the possibility of involvement of other joints. Usually, in taking a history, we ask the patient indirect questions, inquiring about arch supports, lumbago or sciatica, and in this manner we frequently find that the presumed monoarticular disease is a

process. We can therefore focus most of our attention on the findings in the knee. The original symptoms followed an injury. This is a common story in joint involvement, regardless of the underlying process. A meniscus was removed at a previous operation, but there is no information concerning the pathology at that time. I am particularly interested in knowing if the synovial fluid was hemor-

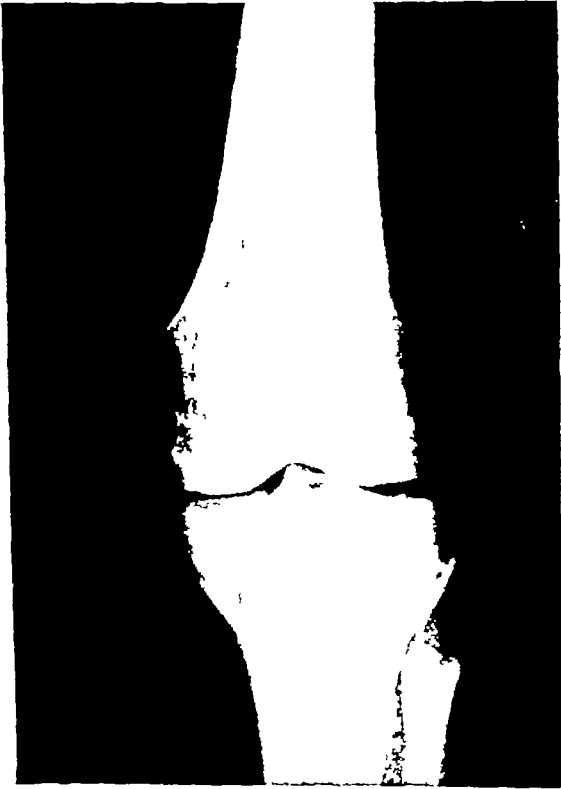


FIGURE 1

part of a generalized type of joint involvement. However, on the basis of the information we have been given we will start with the assumption that this process was localized in one joint. It is also noted that there were no constitutional manifestations such as fatigue, weight loss or fever to indicate that this monoarticular joint involvement was related to a systemic disease such as rheumatoid arthritis or a chronic infectious



FIGURE 2

rhagic or not at that time. That operation apparently did not result in much improvement.

As far as the laboratory work is concerned, two facts may be significant. The sedimentation rate was elevated, and the blood Hinton test was positive. A negative tuberculin test in a dilution of 1:100,000 is not significant because joint tuberculosis can be present with a negative test using even higher concentrations.

May we see the x-ray films?

DR. STANLEY M. WYMAN: We have a single set of films taken of both knees, and they show the prominence of soft-tissue shadows adjacent to the left knee, particularly on the medial aspect and, to a lesser extent, laterally. This is well seen extending posteriorly to the joint. I believe the nature of the soft tissue is more consistent with a

mass than with fluid in the joint space or simply thickening associated with infection. The cortical surfaces of the left knee appear preserved, but there is extensive osteoporosis in the femur and in the tibia particularly on the femoral side in the region of the condyles. There are tiny areas of increased density within the soft-tissue mass, which suggests flecks of calcification.

DR CLARK: There are a number of lesions that might be considered. In spite of the absence of constitutional manifestations, we must consider the possibility of monoarticular rheumatoid arthritis. It is difficult to make such a diagnosis during a small segment of the course of the illness. Usually, such a conclusion is based on following the patient for a period and by eventually ruling out other possibilities. The anteroposterior x-ray film reveals changes in the bones consistent with that diagnosis. However, the periarticular thickening is more than one would expect in rheumatoid arthritis, in spite of the fact that synovial tissue proliferation is a basic part of its pathology. Furthermore, the subchondral destruction in the lateral view is more complete and more localized than we usually see in rheumatoid arthritis. Tuberculosis of the knee must be considered in this differential diagnosis. The x-ray films do not suggest an infectious process, and tuberculosis is not indicated by systemic manifestations. The marked soft-tissue swelling is against that diagnosis. Syphilis must be mentioned. Almost every form of joint disease has been attributed to this infection. I suspect that much of the syphilitic arthritis reported in the literature is actually related to rheumatoid arthritis. Gummas of the joint do occur, and they are in almost all cases related to bone. In my experience, the 2 proved cases of syphilitic involvement of the knee have been gummas of the patella. The problem of Clutton's joints (arthritis associated with congenital syphilis) need not be considered in spite of the presence of apparently healed interstitial keratitis. The fourth diagnosis we have to consider is tumor. I give greater weight to this possibility after seeing the great amount of thickening in the x-ray films. There are two types one might encounter in joints. The first is the benign giant-cell tumor of synovia, usually referred to now as pigmented villonodular synovitis. For those not familiar with this terminology, in relation to benign synovial tumors, I would like to give a word of explanation. Pigmented villonodular synovitis is a term applied by Jaffe¹ to the yellowish-brown, tumor-like lesion of the synovial membrane reported in the literature since 1865. This lesion has also been called benign giant-cell tumor of the synovial membrane, xanthoma, xanthogranuloma, xanthomatous giant-cell tumor and myeloplaxoma. Its morphology is well known to pathologists. We have recently analyzed 10 such cases here. The patients were of both sexes. The

ages ranged between seventeen and eighty years. The duration of symptoms had been from a few hours to fifteen years. There was monoarticular involvement in all cases, with a knee involved in 70 per cent. The patients usually complained of recurrent joint pain. X-ray changes were present in 30 per cent. The characteristic finding was bloody synovial fluid with counts ranging from 28,000 to 2,000,000 red blood cells per cubic millimeter.

The second type of tumor is the synovioma or synovial-cell sarcoma. This is not a common tumor, and I have had very little experience with it. I have drawn chiefly on the literature for information.² The synovioma can produce this picture with these symptoms. I am not so certain about the x-ray findings of bone destruction. The synovioma is not ordinarily confined to the joint cavity, and may extend beyond the joint into adjacent structures.

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DR BENJAMIN CASTLEMAN: Yes.

DR CLARK: We have been inclined to assume that the decalcification in pigmented villonodular synovitis is analogous to the decalcification that occurs in hemophilic arthritis. I would like to explain its symptoms by repeated joint apoplexies. Whether the atrophy comes from disuse or an autonomic phenomenon, we do not know. I agree that this does not appear to be the decalcification of something eroding into the bone or eroding within the bone.

DR MARIAN ROPES: Essentially I used the same type of reasoning as Dr Clark. I first thought of tuberculosis and rheumatoid arthritis. I tended at that time to rule out tumors on the fact that the patient had had two operations. Later, when we found that biopsy had not been done at either operation, a thing that occurs too commonly in opening a joint, I considered villonodular synovitis the most

likely diagnosis. Again, I ruled out malignant tumor, partly on the duration of the course.

CLINICAL DIAGNOSES

Traumatic synovitis
Villonodular synovitis?

DR CLARK'S DIAGNOSIS

Pigmented villonodular synovitis (benign giant-cell tumor of synovia)

ANATOMICAL DIAGNOSES

Synovioma of left knee, with metastases to vertebrae, clavicle, ribs, pelvic bones, peritoneum, abdominal lymph nodes, lungs and liver

Compression myelitis, twelfth dorsal vertebra
Decubitus ulcer, sacral region
Cystitis, acute and chronic, severe
Bronchopneumonia
Interstitial keratitis

PATHOLOGICAL DISCUSSION

DR TRACY B. MALLORY: This knee was explored by Dr. Edwin F. Cave, who found a marked thickening with papillary excrescence of the synovial membrane. Some of the nodular excrescences showed a brownish, chocolate-colored staining, rather suggestive of villonodular synovitis. Microscopical sections, however, did not look like that, and we were inclined to think that we were dealing with malignant neoplasm, although it did not look like any synovioma that we had seen, and we were unable to name it. We sent the slides to Dr. Jaffe, who said he did not know what it was and thought that it was probably a granulomatous lesion, although he could not rule out malignant tumor. We also sent them to Dr. Granville Bennett, who said that he thought it was tumor but did not know what kind of tumor.

The patient at that time refused amputation and was permitted to go home after partial excision and fusion of the knee joint. Pain continued and became so severe that she returned a couple of months later and consented to amputation. At that time very extensive neoplastic involvement of the remnant of the knee joint was found. Once again she was allowed to go home, and a few months later developed evidence of metastases in the lower spine, with transverse myelitis. She finally died of complications of the myelitis. At autopsy we found metastatic lesions in the bones, including the ribs and several vertebrae. There was one minute nodule in the lung, one in the liver and many serosal implants throughout the peritoneal cavity, one of which had invaded the ovary, and

a great many retroperitoneal nodes were involved. The distribution of the metastases was a most unusual one for any form of tumor. The metastases are no easier to classify than the primary tumor. Synoviomas, as I have seen them, surprisingly rarely show very much fibrous tissue, and yet this tumor was, in places, quite scirrhous. Characteristically, they show two types of cells, one of which appears epithelial, the other is spindle-shaped and suggests primitive mesenchyme. There are often clefts in the tumor that appear to be lined with the epithelial elements. I could find no such areas in this case. A rather noticeable feature about this tumor was that many of the cells were coarsely vacuolated. We thought briefly of liposarcoma, but fat stains were negative. Some glycogen was demonstrated in the vacuoles. Neither the character of the cells nor the general architecture of the tumor corresponds to what is ordinarily seen in synovioma. Yet the primary location of the tumor in the synovia of a knee joint is characteristic. I think synovioma is the diagnosis we have to make, despite the rather atypical histologic appearance. Our experience with synoviomas is that they have all been very highly malignant, and early metastases have been the rule.

There was one very interesting phenomenon, which I have never noted before. On the edge of the metastases in the liver and lung the neighboring parenchymal epithelial cells had been stimulated to marked growth. In the lung, for instance, the neighboring alveoli showed a lining of high columnar epithelial-like pulmonary epitheliomatosis. In the liver there was marked proliferation of bile-duct epithelium all around the metastasis as if some growth-stimulating substance were being excreted by the tumor. The fact that this phenomenon was seen in two different organs, each time in close approximation to a metastatic nodule, makes me believe that it was not coincidence. I think there must have been some such peculiar growth stimulation associated with this tumor.

A PHYSICIAN: If a biopsy had been taken at the first operation, it would have helped the treatment, would it not?

DR MALLORY: If the diagnosis could have been made on the original operation, which I think is doubtful in view of the fact that several months later three pathologists disagreed on the diagnosis, immediate amputation might have made a difference. Some six months was lost in this case.

DR CLARK: Most people ignore their lame knees until a diagnosis is of very little help if it turns out to be a malignant tumor.

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- 1 Jaffe, H. L., Lichtenstein, L., and Sutro, C. J. Pigmented villonodular synovitis, bursitis and tenosynovitis. *Arch. Path.* 31: 731-765, 1941.
- 2 Bennett, G. A. Malignant neoplasms originating in synovial tissues (synoviomas). *J. Bone & Joint Surg.* 29: 259-291, 1947.

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in such a case as this may be regarded as practically pathognomonic. And the third is the fact that an apparently satisfactory barium enema was repeated on the following day. This suggests that the Surgical Service was anxious to learn whether spontaneous reduction had occurred or possibly that they hoped to be able to reduce the intussusception by hydrostatic pressure. From the appearance of the films I judge that reduction did not occur.

We must now consider the causes of intussusception in adults. The acute, spontaneous condition observed in children is very rarely, if ever, seen in adults. Furthermore, the recurrent nature of this man's complaint, as well as the presence of diarrhea with blood persisting between the acute episodes, makes me believe that there was some underlying, intrinsic lesion in the bowel that precipitated the intussusception.

Apparently the commonest cause of this condition is submucous lipoma of the colon.* Bloody diarrhea can occur in this condition if there is ulceration of the mucosa overlying the tumor. Benign polyps of the colon have been described as the precipitating factor in intussusception in adults. Carcinoid of the ileocecal region has also, I believe, been described in this relation. I see no reason why any benign tumor of the colon, or possibly of the terminal ileum, might not have been at the root of this man's trouble. The same statement may be made of Meckel's diverticulum. However, I do not see how we can arrive at a positive conclusion concerning just what the lesion was.

On a statistical basis I shall say that submucous lipoma of the cecum or ascending colon is the most likely diagnosis, with mucosal ulceration and intussusception.

DR F THOMAS GEPHART: This patient's history suggested regional ileitis. When the Surgical Service first saw the patient he had developed this large, midepigastic mass and had the barium-enema findings of intussusception. It seemed unusual to see such a large mass result solely from intussusception without more marked signs of acute

intestinal obstruction. This was one point in favor of the diagnosis of carcinoma of the transverse colon. We realized the patient might well have an intussusception, but since he had no signs of acute obstruction, we decided to prepare him for bowel surgery for two days with antibiotics, start a Miller-Abbott tube and transfuse him, watching carefully for signs of obstruction.

After induction with ether anesthesia the large, midepigastic mass had disappeared, and a small firm mass could be felt in the right lower quadrant. At operation the intussusception was found to be reduced, and a hard, doughnut-shaped tumor was found involving the cecum near the ileocecal valve. Though the tumor completely surrounded the bowel, the lumen was not obstructed.

CLINICAL DIAGNOSIS

Carcinoma of the colon, with intussusception?

DR GIDDINGS'S DIAGNOSIS

Submucous lipoma of cecum, with intussusception

ANATOMICAL DIAGNOSIS

Adenocarcinoma of cecum, with previous intussusception

PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN: In the cecum surrounding the appendiceal orifice was an elevated, indurated and ulcerated circular tumor about 5.5 cm in diameter. The appendiceal os protruded into the center of the tumor. The appendix itself was slightly thickened. Microscopically, the tumor was the usual adenocarcinoma, invading but not extending through the muscularis. The ileocecal valve was not involved, nor were any of the regional lymph nodes.

Usually when a carcinoma produces intussusception it is the polypoid type. I suppose in this case the slight involvement of the muscularis and perhaps the unusual location of the tumor contributed to the mobility of the bowel. The intussusception must have included the appendix.

*Pack G T and Booher R J: Intussuscepting submucous lipoma of right colon. *Surg Clin North America* 27:361-372, 1947.

CASE 35122

PRESENTATION OF CASE

A thirty-eight-year-old man was admitted to the hospital complaining of cramps, diarrhea and weight loss.

The patient was in good health until one month before admission, when crampy, right-lower-quadrant pain, accompanied by right-lower-quadrant distention, appeared. This was occasionally associated with vague, left-upper-quadrant epigastric distress. The episodes were intermittent and occurred at any time of the day or night and were sufficiently severe to prevent sleep. There was no relation to eating. Some relief was obtained from belching or bowel movements. Until the onset of the illness he had been chronically constipated. A month before admission the bowel movements became loose and watery, and he had five or six diarrheal stools daily, which contained a few flecks of bright-red blood without pus or mucus. These symptoms lasted for five days and then disappeared for two weeks, when they recurred and gradually became more severe. The appetite diminished. On the night before admission he vomited for the first time. During the past year his weight went from 135 to 118 pounds because he did not have enough to eat.

His father was living, aged seventy-five, and had been operated upon eight years previously for "cancer of the stomach." A brother had been operated on for "cancer of the rectum" several years previously.

Physical examination showed an undernourished, underdeveloped man. The abdomen was moderately distended, and the lower half was tympanitic, more on the right than the left. The peristaltic sounds were normal. There was considerable direct and rebound tenderness in the right lower quadrant, with voluntary spasm. No mass was felt. There was mild bilateral costovertebral-angle tenderness. The left testicle was undescended, and a partially reducible left direct inguinal hernia was present. On rectal examination hemorrhoids were found and there was marked tenderness in the right vault, but no mass was felt.

The pulse was 88, and the respirations 20. The blood pressure was 120 systolic, 80 diastolic.

Laboratory examination demonstrated a normal urine. The white-cell count was 8800, with 88 per cent neutrophils. The hemoglobin was 12 gm. The stools were liquid, brown and guaiac positive. The serum protein, prothrombin time and cholesterol were all within normal limits. X-ray study of the chest demonstrated no abnormality. In the abdomen a plain film suggested a mass in the right upper quadrant, partially outlined by gas within the colon. On barium enema the barium flowed to the midtransverse colon, where a complete obstruction was met. Barium flowed along the margins of a lu-

menal mass for a short distance. There was a large palpable mass in this area. A sigmoidoscopic examination showed no abnormalities, but "the bowel seemed a bit spastic."

On the second hospital day a mass was felt to the right and below the umbilicus. On the following day it had moved to the left half of the abdomen to the level of the umbilicus.

An operation was performed five days after admission.

DIFFERENTIAL DIAGNOSIS

DR. W. PHILIP GIDDINGS: The salient points of this history are that the patient was a man of thirty-eight years whose symptoms were of one month's duration. There appear to have been two different sets of symptoms, both referable to the lower gastrointestinal tract. The first consisted of intermittent diarrhea with five or six loose stools daily and with small amounts of bright blood in the stools. The second comprised episodes of right-lower-quadrant pain of significant severity, accompanied by right-lower-quadrant distention, partially relieved by eructation or defecation and apparently attended by vomiting the night before admission.

There was a suggestive family history of gastrointestinal cancer. Physical findings directed attention to the right lower quadrant and were compatible with ileus. Under observation there was a palpable mass in the right lower quadrant, which twenty-four hours later had moved to the left side. Proctoscopy was negative, and the presence of blood in the stools was confirmed. Blood chemical findings were normal. The polymorphonuclear leukocytosis suggested an inflammatory component to the disease, but we do not know whether or not there was fever.

The finding of hernia and cryptorchidism on the left raises the question whether or not either might have been related to the present illness. However, the reducibility of the hernia rules it out as a source of trouble, and the likelihood that a tumor in an undescended left testis would cause primarily right-sided bowel symptoms seems small. I believe these conditions were not related to the present illness.

The barium-enema films are revealing. There was a convex defect in the midtransverse colon, with the margins of an obstructing, fairly smooth, intraluminal mass clearly outlined. This appearance was the reverse of the concavity with "shelf" formation commonly seen in carcinoma of the colon. It is, however, characteristic of intussusception.

In addition to the x-ray appearance, there are three reasons for believing that this man suffered from intussusception. The first is the recurrent nature of the acute episodes, with intervals of relief, suggesting repeated bouts of a process that relieved itself.

The second is the observed migration of a mass from the right to the left side of the abdomen, which

the people. The second is that governmental agencies must acknowledge and discharge their statutory obligations and that, in the instances covered by the present study, the communities of Greater Boston should accept all the financial aid that federal and state laws make possible.

The fiscal troubles in which the social and health services of the area find themselves are due to a variety of causes, and a variety of remedies, some of them drastic, are necessary to correct them. The failure mentioned above of governmental agencies, "charged with the legal duty to render certain services to people who meet clearly stated conditions," is an important cause, and it is appropriate to note that Greater Boston has received a smaller percentage of help from federal sources than the other areas with which it was compared — 94 per cent against an average of 118 per cent. Voluntary agencies should not use voluntary funds to pay for such services.

As corollaries to this principle, it should be established that when the provision of certain services has become widely accepted as a proper duty of government, it is mistaken community policy to support such services indefinitely from limited voluntary contributions, and that tax-supported agencies obtaining service from voluntary agencies should fully reimburse those agencies for the services received.

Needless duplication and overlapping of services, as they now exist, should be done away with, agencies should combine in some instances and should transfer their functions to competitive agencies and go out of business in others. Some services now supported by voluntary community funds should become self-supporting.

The Survey finally recommends that at the highest level a strong central agency should be established for fund raising, planning and budgeting, to replace its excellent but less adequate parents, the Greater Boston Community Fund and the Greater Boston Community Council.

In an area where "some of the newest and some of the oldest methods, and certainly some of the most tenacious traditions, in American public welfare and public health" exist, among more than 800 agencies, reforms may be difficult to institute. The

very number of agencies involved, however, indicates the inefficiencies that must be remedied. The writing on the wall is in red ink and is preceded by a dollar sign.

DISREGARDED SEEDBED OF THE TUBERCLE BACILLUS

For adequate control or eradication of a disease like tuberculosis it is essential to know the sources of the infection and how it is spread from those sources. The steady decline in mortality figures is usually interpreted as indicating that the sources of infection are becoming fewer and that the disease is becoming of minor importance. Studies in certain limited population groups, however, have indicated that incidence and mortality are actually independent of each other and that the amount of clinically active tuberculosis is the result of these two. Only a small proportion of attempts to determine the "source case" for any new patient with tuberculosis are successful, and this must mean that the majority of new cases arise from clinically unimportant or clinically unrecognized sources.

Medlar and his co-workers* attempted to discover some of the unrecognized sources through a careful study and analysis of the autopsy material from Bellevue Hospital. The large and varied clinical and autopsy material seen at that hospital offered an excellent opportunity to determine on the one hand the incidence of deaths from tuberculosis and on the other the incidence of unhealed tuberculosis in persons who died from other diseases. They analyzed the post-mortem data of all patients over fifteen years of age for the ten-year period, 1935-1944, in relation to age, sex, race, the presence or absence of caseous foci or cavities in the lungs, generalized miliary tuberculosis and tuberculosis as a primary cause of death or as an incidental finding in persons who died of other diseases and the clinical diagnosis in relation to the recognition of the tuberculosis that was found at autopsy. They looked particularly for caseous foci in the lungs, as indicated by areas of necrotic tuberculous pneumonitis, which, when they soften and are extruded, serve as a source from which tubercle bacilli may be

*Medlar E. M., Spain D. M. and Holliday R. W. Disregarded seed-bed of tubercle bacillus. *Arch. Int. Med.* 81:501-517 1948.

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GREATER BOSTON COMMUNITY SURVEY

IT HAS been apparent for some time that the per-capita expenditure for charitable purposes in Greater Boston has been more generous than in a number of comparable areas. It has not been so apparent that the returns from each of the multiplicity of agencies involved has always been on a commensurate scale. A multiplicity of competitive appeals has developed, moreover, each of which makes its demands upon the public conscience and the public purse. When the dollars themselves, in addition to shrinking in value, began to shrink in numbers, it seemed obvious to certain persons interested in the Greater Boston Community Fund and the Greater Boston Community Council that something should be done about it.

Accordingly, Robert Cutler, well known for his interest in the public welfare, was invited early in 1947 to form a committee of citizens to investigate the problem. This committee of 180 persons met in March, two years ago to launch the enterprise. The result was the Greater Boston Community Survey of the more than 800 voluntary and tax-supported agencies in 55 of the independent communities that make up the non-political and vaguely defined area known as Greater Boston.

The basic object of the Survey has been "to make sure that the charitable dollar annually raised in Greater Boston does the greatest good for the greatest number in the most economical, effective way." It has been carried on and its results finally approved by an executive committee of 16 members, who, at the beginning of their labors, selected Robert P. Lane, of New York, as director of the Survey. The report of the Survey has been accepted by the Committee of Citizens.

The task has been difficult and many of its problems unprecedented. As the director stated in his foreword to the final summary report, recently issued:

In the cities and towns of Greater Boston are found some of the country's oldest voluntary agencies, a few of them with some of the country's largest capital reserves, agencies established and for decades supported by persons bearing names that are honored throughout the country. Here are agencies that march in the forefront of advancing professional practice. Here are agencies that were once distinguished pioneers in important fields, still unforgetful of their early glory. Here are some of the newest and some of the oldest methods, and certainly some of the most tenacious traditions, in American public welfare and public health. Here in these independent, self-governing communities, are found a local pride, a resistance to outside control, a determination to manage one's own affairs, that are the very pith of the American spirit. Tax-supported and voluntary alike, the social and health agencies of Greater Boston present both an unparalleled opportunity and an unparalleled challenge to any group of lay citizens and professional workers who undertake a survey of this ancient, complex and justly proud community.

The director further stated two "preconceptions" that might be accepted as basic principles wherever the activities and the support of any social agency are scrutinized. The first is that all agencies, regardless of their auspices and the source of their funds, are engaged on a common task for the benefit of all.

the people. The second is that governmental agencies must acknowledge and discharge their statutory obligations and that in the instances covered by the present study, the communities of Greater Boston should accept all the financial aid that federal and state laws make possible.

The fiscal troubles in which the social and health services of the area find themselves are due to a variety of causes, and a variety of remedies, some of them drastic, are necessary to correct them. The failure mentioned above of governmental agencies, "charged with the legal duty to render certain services to people who meet clearly stated conditions," is an important cause, and it is appropriate to note that Greater Boston has received a smaller percentage of help from federal sources than the other areas with which it was compared — 9.4 per cent against an average of 11.8 per cent. Voluntary agencies should not use voluntary funds to pay for such services.

As corollaries to this principle, it should be established that when the provision of certain services has become widely accepted as a proper duty of government, it is mistaken community policy to support such services indefinitely from limited voluntary contributions, and that tax-supported agencies obtaining service from voluntary agencies should fully reimburse those agencies for the services received.

Needless duplication and overlapping of services, as they now exist, should be done away with, agencies should combine in some instances and should transfer their functions to competitive agencies and go out of business in others. Some services now supported by voluntary community funds should become self-supporting.

The Survey finally recommends that at the highest level a strong central agency should be established for fund raising, planning and budgeting, to replace its excellent but less adequate parents, the Greater Boston Community Fund and the Greater Boston Community Council.

In an area where "some of the newest and some of the oldest methods, and certainly some of the most tenacious traditions, in American public welfare and public health" exist, among more than 800 agencies, reforms may be difficult to institute. The

very number of agencies involved, however, indicates the inefficiencies that must be remedied. The writing on the wall is in red ink and is preceded by a dollar sign.

DISREGARDED SEEDBED OF THE TUBERCLE BACILLUS

FOR adequate control or eradication of a disease like tuberculosis it is essential to know the sources of the infection and how it is spread from those sources. The steady decline in mortality figures is usually interpreted as indicating that the sources of infection are becoming fewer and that the disease is becoming of minor importance. Studies in certain limited population groups, however, have indicated that incidence and mortality are actually independent of each other and that the amount of clinically active tuberculosis is the result of these two. Only a small proportion of attempts to determine the "source case" for any new patient with tuberculosis are successful, and this must mean that the majority of new cases arise from clinically unimportant or clinically unrecognized sources.

Medlar and his co-workers* attempted to discover some of the unrecognized sources through a careful study and analysis of the autopsy material from Bellevue Hospital. The large and varied clinical and autopsy material seen at that hospital offered an excellent opportunity to determine on the one hand the incidence of deaths from tuberculosis and on the other the incidence of unhealed tuberculosis in persons who died from other diseases. They analyzed the post-mortem data of all patients over fifteen years of age for the ten-year period, 1935-1944, in relation to age, sex, race, the presence or absence of caseous foci or cavities in the lungs, generalized miliary tuberculosis and tuberculosis as a primary cause of death or as an incidental finding in persons who died of other diseases and the clinical diagnosis in relation to the recognition of the tuberculosis that was found at autopsy. They looked particularly for caseous foci in the lungs, as indicated by areas of necrotic tuberculous pneumonitis which, when they soften and are extruded, serve as a source from which tubercle bacilli may be

*Medlar E. M., Spain D. M. and Holliday R. W. Disregarded seed-bed of tubercle bacillus. *Arch. Int. Med.* 81:501-517 1945.

scattered within the lung and to the outside world. Since the results of this analysis are most revealing, some of the highlights are summarized.

With respect to race they found that in most cases in which tuberculosis was recorded in the autopsy records of Negroes it was the primary cause of death, whereas 29 per cent of white patients died from diseases other than tuberculosis. This suggests that if progressive tuberculosis becomes established in Negroes, they seldom survive long enough to die of other causes, whereas white persons often do. For that reason caseous foci were often mentioned as incidental findings in white patients.

With respect to age, it was found that tuberculosis was the cause of death in all patients under thirty years in whom unhealed tuberculous lesions were recognized, but the disease was the cause of death in only half the patients over seventy years old. Tuberculosis was diagnosed clinically in 89 per cent of the cases in which it was the primary cause of death. This varied with the age, however, for it was diagnosed in about 97 per cent of those under thirty years of age and in only 60 per cent of those over seventy years. Even in cases of tuberculous cavities in the lungs the diagnosis was made in only 70 per cent of the patients over seventy years of age. There was a general decrease in the clinical diagnosis of tuberculosis with the increase of the age of the patient.

It was also evident from these data that unhealed tuberculosis received little clinical attention in persons who died from other diseases. The clinical diagnosis of tuberculosis was recorded in less than half such patients with tuberculous cavities in the lungs.

The Bellevue pathologists also compared their autopsy data with the mortality figures for the same period for persons over fifteen years of age throughout the City of New York. The hospital material contained a somewhat lower proportion of persons over seventy years old. Proved tuberculous deaths in all ages were twice as frequent in the autopsy series as in the City series. The ratio between the Bellevue figures and those from the City was 1.4:1 for patients under thirty years and 3.9:1 for those over seventy years. About three fourths of the autopsied cases from Bellevue Hospital in patients

under sixty years of age who died from tuberculosis were from the special service for the treatment of diseases of the chest, whereas in the group over seventy years of age, more than two thirds of the cases were from other services. It therefore seems that the higher proportion of deaths from tuberculosis at Bellevue was not due solely to the fact that there is a large active service for chest cases in that hospital.

Another interesting observation emerged from a comparison of incidence of unhealed tuberculosis among autopsies in two periods — namely, from 1920-1922 and from 1940-1942. Since the mortality figures from tuberculosis declined markedly in this interval, it was expected that the incidence of unhealed tuberculosis in the autopsy material would show a corresponding decline. The data, however, showed little change in incidence of unhealed tuberculosis, but instead there was a shift in the age distribution of these lesions, there being proportionally fewer cases under fifty years of age in the latter period. This tends, of course, to reflect the trend in the aging in the population.

A comparison of two samples of data from the same generation — that is, those who were fifteen to twenty-nine years old in 1920-1922 and those who were thirty to forty-nine years of age in 1940-1942 — revealed two points. As the generation aged, the ratio of deaths from other diseases to the deaths from tuberculosis increased, and, in patients with unhealed tuberculous lesions, there was a decrease in the ratio of deaths from tuberculosis to deaths from other causes. Thus, the greater incidence of unrecognized disease in old people must be considered not only the result of the holdover of patients who survived from the time when the mortality (and presumably the incidence in young people) was high but also due to new cases occurring in older age groups.

Confirmatory evidence for this conclusion is also quoted from experiences of the Metropolitan Life Insurance Company, where employees originally having negative x-ray examinations and tuberculin tests have been followed for a number of years. The average age when these persons began their employment was twenty years, and yet 63 per cent of them were found to have acquired the disease from one to

ten years later. Moreover, 10 per cent were employed for over fifteen years before acquiring tuberculosis. A history of contact with known cases was elicited in only about 10 per cent of these new cases. Medlar and his associates believe, on the basis of their autopsy experience, that these infections are new ones acquired in adult life rather than latent ones too minute to be detected earlier. This is a good illustration of increments of tuberculosis in an adult population that was as free from demonstrable tuberculosis as it is possible to determine from x-ray studies.

In discussing their observations, Medlar and his co-workers bring out the fact that today the majority of persons ill with tuberculosis are restored to a state of clinical well-being and many survive for years to die eventually from some other cause. Throughout their life many of these persons continue to shed tubercle bacilli and thus constitute one part of the seedbed of this disease.

Data are also quoted to show that tuberculosis is not too well controlled. About two thirds of the deaths from tuberculosis in a single year in New York City occurred outside any hospital, and another third took place within a month of admission to a hospital. A significant proportion of patients with active tuberculosis leave the hospitals against medical advice, and many patients are admitted to the hospital only for clinical relapse of the disease. Furthermore, about 1 in every 8 newly discovered cases first becomes known through death registrations, and about half the patients with tuberculosis are discharged from hospitals either improved or unimproved. All these facts also relate to that part of the seedbed which is known.

The fact that unhealed tuberculosis is seldom found in the autopsy records of adults under thirty years of age when death was due to other diseases suggests that, if unaltered in its course, progressive tuberculosis is a highly fatal disease in young adults. The finding of unhealed lesions in increasing numbers of persons dead from other diseases, in proportion to those dead from tuberculosis, indicates that a progressive infection acquired in later life tends to be less explosive. Tuberculosis is therefore less likely to be suspected in persons over fifty years of age. This constitutes the unknown part of the

seedbed, which the autopsy data indicate contains approximately 1000 persons with cavity formation per 100,000 of the population.

According to these workers control of tuberculosis—that is, the decrease in the continuity of the disease—requires intelligent supervision of the seedbed to prevent the return to the soil of the factors that favor the tubercle bacilli. This means a planned follow-up study of all persons with unhealed disease, including those with x-ray shadows, regardless of whether their disease is considered active or inactive. In addition, an intensified search must be made for a cure, in a pathological as well as in a clinical sense, of those who have a progressive disease. “The seedbed must be eradicated if tuberculosis is to be eradicated.”

AMORY PRIZE AWARDS

THE American Academy of Arts and Sciences is the custodian of a substantial sum of money, the interest of which is available each seven years for the award of the Francis Amory Prize to one or more persons who in the preceding septennium have made notable contributions to the “treatment and cure of diseases and derangement of the human sexual generative organs in general, and more especially for the cure, prevention, or relief of the retention of urine, cystitis, prostatitis, etc.” It was the expressed wish of the donor that the prize be awarded preferably for some “cunning contrivance or invention,” but if such an invention was not forthcoming, other means to the desired end might be recognized.

The awards for the preceding septennium were conferred at a meeting on December 8, 1948, by the president of the Academy, Howard Mumford Jones, and Professor E. B. Wilson, chairman of the Amory Prize Committee. A cash prize of \$3500 was presented to each of six distinguished investigators. Dr. Alexander B. Gutman, of New York City, Dr. Charles B. Huggins, of Chicago, Dr. Willem J. Kolff, of Kampen, Holland, Prof. Guy C. Marnan, of Edinburgh, Dr. George N. Papanicolaou, of New York City, and Dr. Selman A. Waksman, of New Brunswick, New Jersey.

In commenting on the work of these scientists, Dr Huggins, who made the principal address of the occasion, emphasized the close similarity between scientists and artists both are devoted to the creation of orderliness and the search for truth among a host of confusing details. Like other forms of art, science can be dull or elegant, but good science is capable of evoking the highest intellectual pleasure in its creator and his auditors. "Good science finds itself equally at home in an institute of the Arts as of the Sciences."

"Medical research differs from the purer but not necessarily more elegant branches of science in the peculiarity that human beings with illness are its essential reason for being." And despite the necessity for quiet and leisurely reflection for creative thought the investigation should always be mindful of the sick patient in the background.

Urology was set forth as one of the youngest of the developed medical specialties—one of the finest accomplishments of this age, there is now no urologic illness that cannot in some way be improved by therapy. "Within the past ten years the treatment of venereal disease—a tremendous problem—has been solved." Nevertheless, the genitourinary system is extremely vulnerable to disease—mostly infections and tumors, which at one time or another afflict more than half of all human beings, hence, much more research remains to be done.

Among the 1948 recipients of the Amory prize, Dr Gutman is notable for the discovery of the usefulness of serum acid phosphatase determinations in the diagnosis and management of malignant prostatic neoplasms. Dr Huggins's splendid work on the influence of several hormones on prostatic secretion and on the diagnosis and treatment of cancer of the prostate is of world-wide renown. Dr Kolff, following up the work of Abel, Rowntree and Turner, of Johns Hopkins, has developed a practical "artificial kidney" for the treatment of acute uremia. Prof Marrian shared in the Amory Awards because of his searching investigations of steroid hormones that affect the functions of the generative tract, leading to important diagnostic and therapeutic measures. Dr Papanicolaou's work on exfoliative cytology is coming to be widely

applied not only to the diagnosis of cancer in the organs of the genitourinary tract but also to malignant growths in the hollow organs generally. Dr Waksman's discovery of streptomycin has been a major factor in the triumphs of current urologic therapy.

Dr Huggins concluded his Amory address with the following stirring words:

We are all impressed by the vigor and power of the human mind as demonstrated by the use of the scientific method. Science is not concerned with whether its products are constructive or destructive, its only proper interest is in establishing truth. The velocity of scientific development in this age is tremendous. In the field in which Francis Amory was interested, God only knows what the next septennium will bring forth, but I can guarantee that it will be good news for sick people, if we can survive the prescriptions of the politicians.

The Amory Committee will welcome nominations for Awards for suitable work done in the current septennium ending in November, 1955.

DISASTER IN CHILE

IN NOVEMBER, 1948, the library of the medical school and the department of parasitology of the Chilean Public Health Service were burned to the ground in a great fire. The scientific equipment, museum specimens, slides, colonies of insects and books and periodicals were completely destroyed. The Department of Parasitology is seeking the cooperation of the scientific world in the task of rehabilitating its collections for the purposes of teaching and research. There is great need of parasitology specimens, mounted or unmounted, histologic sections and insects and arachnids. Medical literature on the subjects of parasitology, biology, public health in general, epidemiology, vital statistics, rural health and health education, including reprints, is urgently needed. A first-class periodical entitled the *Revista chilena de higiene y medicina preventiva* is published at Santiago. The address for the present is Departamento de parasitologia, Cassilla 9183, Santiago, Chile.

The Boston Medical Library, 8 Fenway, Boston 15, in view of the magnitude of this disaster, is prepared to receive literary material, if sent prepaid, and arrange for its transportation to Chile. To avoid duplication, lists of available material should be sent to the Library before shipment.

MASSACHUSETTS MEDICAL SOCIETY

PRINCIPLES AND PROPOSALS

The following principles were adopted on February 9, 1949, by the Committees on Medical Economics and Public Relations of the Massachusetts Medical Society for presentation at the meeting of the Planning Committee of the American Medical Association on February 12, 1949

1 We believe that the health of the people served by prepayment insurance plans will be most benefited by medical care free of government administration and control

2 We should like to call attention to the profligate waste and duplication in health programs operated by the government in regard to both hospital beds and personnel as reported by the Hoover Commission. We believe that compulsory health insurance operated by the Government would result in similar inefficiency

3 We believe that the manner of expression of policy on the part of the American Medical Association has served to diminish public confidence in that body to the serious concern of many of the members of the association

We believe that the policy of the American Medical Association should be one of more active and enthusiastic support of constructive proposals for more equitable distribution of medical care

Therefore, we suggest as constructive proposals worthy of support the following

1 The objective of adequate medical care in our free society is to make available to everyone — regardless of race, color, creed, financial status or place of residence — every known essential preventive, diagnostic and curative medical service of high quality. The attainment of such medical care must necessarily be an evolutionary process which will require the co-operation of all concerned over a period of years

2 The principle of voluntary prepayment health insurance should be the basic method of financing medical care for the large majority of the American people, in order to remove the burden of unpredictable sickness costs and abolish the economic barrier to adequate medical services

3 The success of any plan for medical care is dependent on the mutual co-operation of the public, those rendering professional services and the administrative agencies. This co-operation can be obtained only if those rendering the services are convinced that they will have a continuing authoritative voice in the formulation and execution of policies and plans, thereby assuming their proper share of responsibility

4 Voluntary prepayment group health plans, embodying group practice and providing comprehensive service, when practicable, offer to their members excellent medical care. Hence such plans should be encouraged

5 The people have the right to establish voluntary prepayment plans on any basis guarded by legal restrictions, necessary to assure proper standards and qualifications

6 Provision of adequate medical care for those unable to obtain it by voluntary prepayment plans or by direct payment is the responsibility of the local or state government. Part of the burden of this responsibility may be assumed by charitable agencies. Federal grant-in-aid to state programs administered by state boards of health is an acceptable method of helping to meet this responsibility

7 The medical care of those who are able to purchase it by voluntary prepayment plans or by direct payment is the responsibility of the individual

8 The Federal Government should, wherever possible, support voluntary prepayment programs for hospital and medical care

9 Eligibility for receiving benefits under a program aided by federal grants should be determined by the individual states or communities

10 The patient shall have free choice of his physician, group of physicians, clinic or hospital from among those participating in any plan, provided that the physician, group of physicians, clinic or hospital shall have the right to refuse or accept the patient

11 Physicians and other qualified persons rendering medical care shall receive adequate remuneration for their services

12 The physician shall be free to elect or reject without prejudice participation in a medical care plan. The rights of the physician as to the choice of methods by which he is to be paid shall be fully protected

13 We agree that the federal Government now should subsidize medical and nursing education, medical indigents, health and diagnostic centers, including mental, where not now adequate

We believe effective organizations of state and district health councils would immeasurably improve the community concept of local health needs. The initiative of the people themselves, and especially of the medical and public health personnel, must provide the spark

14 The Massachusetts Medical Society looks upon these basic principles as essential to the development of any successful medical-care plan, and as guides by which to evaluate medical-care plans that may be proposed in

the future, with the understanding that changing conditions may require their later revision

We further urge that our delegates to the American Medical Association be instructed to press for the general adoption of the above principles and proposals by the American Medical Association

H QUIMBY GALLUPE, *Secretary*

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- HINMAN, CRAWFORD H, 270 Brookline Avenue, Boston
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- JEWETT, JOHN FIGGIS, 1 Anderson Place, Boston
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- JILLSON, OTIS FIELD, 750 Harrison Avenue, Boston
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- KRAMER, PHILIP, 415 Commonwealth Avenue, Boston
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- DAVIS, LLOYD HAYES, 290 Main Street, Webster
Northwestern University School of Medicine, 1922
- DI MATTEO, ANTHONY P, 11 Hartford Road, Worcester
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- DISTEFANO, ANTHONY JAMES, JR, 296 Oak Street, Shrewsbury
Marquette University School of Medicine, 1945
- JACOBS, NATHAN, 211 Main Street, Fisherville
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- KILROY, EDWARD FRANCIS, 644 Grove Street, Worcester
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- KING, JOSEPH ANTHONY, JR., Worcester City Hospital, Worcester
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- MCCREADY, FREDERICK JOSEPH, 68 Reed Street, Worcester
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- O'DONNELL, ANNE R, 36 Commodore Road, Worcester
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- SACHS, BARNEY EDWARD, 989 Main Street, Leicester
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- SHANNON, PAUL VINCENT, 159 Highland Street, Worcester
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- WATERMAN, GEORGE ELWELL, Box 312, Clinton
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- WITKOW, ALEXANDER, 32 Saxon Road, Worcester
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George Washington University School of Medicine, 1943
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Tufts College Medical School, 1944

grown in numbers and that many more volumes are sent out to hospitals than heretofore. Instead of doctors coming to the Library for books, the books go to the doctor.

We have made some repairs, but more need to be done. The roof has been partially repaired only. There have been some painting jobs done, particularly in the office of the *Journal*, but more bright colors would add considerably and I hope more can be done this year.

In 1950 the Boston Medical Library will be seventy-five years old. It is planned to celebrate its birthday with a dinner at least, and perhaps some other activity. I hope also that a campaign may be started to raise the necessary \$75,000 to complete our much-needed stacks.

I fear I may become tiresome about these stacks but unless they are installed the Library cannot serve its members efficiently. To climb stairs and mount scaffolding to locate volumes in temporary cases is exhausting and takes time. We must soon have the stacks and elevator.

We should continue our effort to increase our fellowships, for, as I have said before, the fellows are the legal corporation of the Library. They are the custodians of its treasures, and the responsibility should rest on many shoulders.

I wish again to express my great appreciation of the work already accomplished by the Librarian and the Director, and I am sure you would wish me to extend your thanks to them also. I want also to thank the Secretary and Treasurer and the members of the Board of Trustees for their whole-hearted co-operation. I think the Treasurer should have a little extra for his several efforts to obtain additional funds. If they come to naught it is certainly no fault of his.

I will leave to the Librarian the pleasant duty of informing you of our recent accessions and of the present state of our collections.

On the whole the prospect looks bright for continued prosperity and usefulness of this collection of books, one of the largest and most valuable medical libraries in the country.

WALTER G. PHIPPEN

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

RETROLENTAL FIBROPLASIA

The National Society for the Prevention of Blindness has circularized directors of maternal and child health with the following material, asking them to bring it to the attention of physicians:

"Retrolental fibroplasia, the presence of an opaque membrane behind the lens, was described by T. L. Terry, of Boston, in 1942 as a cause of blindness among premature infants. In a recent study covering various American cities, the incidence of the

disease in 1301 premature infants weighing less than 1810 gm (4 lb) at birth was 7.6 per cent. It is recommended, therefore, that infants who were below this weight at birth be given a careful ophthalmoscopic examination at the age of six to nine months. Earlier than this the opaque membrane may not be seen except at the extreme periphery of the retina. Ophthalmologists interested in observing the development of the condition may want to see the infants in the early stages to look for dilatation, tortuosity and thickening of the retinal vessels, exudate and evidence of separation of the retina.

"The etiology of retrolental fibroplasia is unknown. Almost all reported cases have occurred in premature infants. Many theories of the causation have been discussed, some relating to the mother's condition during pregnancy, and others relating to nutrition, drug therapy and health of the infant. It is not now believed to be produced by the lights present in incubators.

"Treatment at present is not satisfactory. Some of these babies develop glaucoma and other eye conditions, so that they should be under ophthalmologic supervision."

BIBLIOGRAPHY

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Owens W. C. and Owens E. U. Retrolental fibroplasia in premature infants. *Tr Am Acad Ophthalmol & Otol* 18:41, September-October 1948.
Reese A. B. Retrolental fibroplasia. *Am J Ophthalmol* 31:623-625, 1948.
Terry T. L. Extreme prematurity and fibroblastic overgrowth of persistent vascular sheath behind each crystalline lens: preliminary report. *Am J Ophthalmol* 25:203, 1942.
Terry T. L. Retrolental fibroplasia. *Adv in Pediatr* 3:55-67, 1948.

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The April schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

CLINIC	DATE	CLINIC CONSULTANT
Lowell	April 1	Albert H. Brewster
Salem	April 4	Paul W. Hugenberger
Haverhill	April 6	William T. Green
Greenfield	April 11	Charles L. Sturdevant
Gardner	April 12	Carter R. Rowe
Brockton	April 14	George W. Van Gorder
Worcester	April 15	John W. O'Meara
Pittsfield	April 20	Frank A. Slowick
Fall River	April 25	David S. Grice
Springfield	April 26	Garry de N. Hough, Jr.
Hyannis	April 28	Paul L. Norton

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

CORRESPONDENCE

DEPRIVATION AND RESTORATION OF LICENSES

To the Editor: At the meeting of the Board of Registration in Medicine held February 17, it was voted to revoke the registrations of Dr. Benedict Kudish, 526 Harvard Street, Brookline, and Dr. Allister F. MacDougall, formerly of Westford, and to restore the registration of Dr. Abraham Freitag.

GEORGE L. SCHADT, M.D., Secretary
Board of Registration in Medicine

State House
Boston

DEATHS

BACON — Newton S. Bacon, M.D., of Cambridge, died on March 1. He was in his seventy-seventh year.

Dr. Bacon received his degree from Harvard Medical School in 1899. He was resident physician at Long Island Hospital and was a fellow of the American Medical Association.

A son and a brother survive.

HAND — Edward P. Hand, M.D., of Holyoke, died on January 4. He was in his sixtieth year.

Dr. Hand received his degree from Georgetown University School of Medicine in 1914. He was a former city physician, a member of the staffs of the Holyoke and Providence hospitals and fellow of the American College of Surgeons and American Medical Association.

Three brothers survive.

SKEIRIK — Jibran Y. Skeirik, M.D., of Lawrence, died on December 5. He was in his fifty-fourth year.

Dr. Skeirik received his degree from Harvard Medical School in 1929. He was a fellow of the American Medical Association.

His widow and a daughter survive.

BOSTON MEDICAL LIBRARY

REPORT OF THE PRESIDENT*

At this meeting I complete my term as your president, and it gives me considerable pleasure to present my third annual report on the state of the Library.

When I assumed office it did not take much study to realize that the first great need of the Library was more income. The budget did not balance, and we were drawing heavily on our invested funds, both restricted and unrestricted, to pay current bills. Consequently, economy was the rule, and while the Librarian and the Director did extraordinarily well with a very loyal staff, the service was not so good as might have been expected of a library of our size and reputation. There is, of course, a considerable value in a library building and its contents of books and periodicals, but its real value is in making these books and periodicals available to its members and to the public, in an attractive and prompt way. In other words, the value of a library may be measured in a sense by the circulation of its books and the use of its shelves. This, then, seemed the second objective, to increase the usefulness of the Library.

At the end of three years I am happy to say that the first of these objectives has been attained. When the dilemma in which the Library found itself was clearly presented to the members of the Massachusetts Medical Society, they saw that the Library was a very necessary part of medical education, that its collections should be available to all physicians and, therefore, that it ought to be considered a responsibility of the Society to help promote its efficiency and usefulness. Every fellow of the Mas-

sachusetts Medical Society is now a member of the Library, entitled to its privileges, sharing its responsibility (through its Society-appointed trustees) and contributing to its welfare. This is as it should be. Mr. Conant, speaking of the university library in his annual report, says, "neither teaching nor advanced scholarly studies in the humanities or the social sciences can go forward if a university library suffers from neglect" and I am sure that the same thing is true of medical science and its medical library.

Thanks to this splendid co-operation of the Massachusetts Medical Society the budget is now balanced for the first time in many years. We have paid back a considerable part of our indebtedness to our restricted funds, and with good luck we should be able to clean this up in a year or two at the most. This does not, by any means, put us on easy street. Money must still be saved or raised to complete the much-needed stacks.

Our extra income has enabled us to add several members to our staff, both housekeeping and technical. The extra housekeeping staff has enabled us to apply the mop and duster more efficiently and slowly to clean house. With our extra library staff we have been able to move and sort books that had accumulated in halls, closets and corridors. Some of these have been sold as duplicates, and some put in circulation, and several thousand volumes have been transferred to the Deposit Library on Soldiers Field. We now occupy about two thirds of the space we control in the Deposit Library. This service is rather expensive, but until we can complete the stacks there seems to be no alternative.

Among those added to our staff I might mention Mr. Charles Colby, who comes to us from the Army Medical Library with considerable training and experience in library work. For the present he will have charge of the Reference Room, with special assignments elsewhere as occasion demands and the Director thinks advisable.

I think I can also report considerable progress toward our second objective. In 1945 the use of the Library as measured by circulation was 31,298 volumes. In 1948 it was 53,515, a gain of 22,217 volumes in three years. If measured in terms of attendance the figures are not so dramatic, but even here there was a gain of nearly 3000. Furthermore, it is interesting to note that in 1947, the year before the membership included the fellows of the Massachusetts Medical Society, 9000 nonmembers availed themselves of the privilege of the Library in one way or another. We may therefore say not only that the financial structure of the Library is on a sound foundation but also that its usefulness to the medical profession has been made more available and comprehensive. I think it is fair to say that the smaller increase in attendance compared to the larger growth in circulation is due to the fact that our professional memberships have

*Presented at the annual meeting of the Boston Medical Library, March 1, 1949.

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Number 13

SURVIVAL IN PRIMARY CARCINOMA OF THE LUNG*

RICHARD H. OVERHOLT, M.D.,† AND IVAN C. SCHMIDT, M.D.‡

BROOKLINE, MASSACHUSETTS

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The recent medical literature contains a number of comprehensive accounts that deal with incidence, symptoms and clinical manifestations of the disease, as well as with technical matters of lung excision.⁵⁻⁸ The over-all problem of cancer of the lung has been particularly well presented by Churchill.⁹ A discussion of clinical features is not included in this report.

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From June, 1932, to August, 1948, a total of 604 patients in whom the diagnosis of primary carcinoma of the lung was made were seen. In 481 cases, the diagnosis was supported by microscopical proof. Great care has been taken to include only cases of carcinoma. Dr. Shields Warren and his associates have again reviewed the histologic sections and have

excluded all cases of so-called "malignant" adenoma, adenoma, lymphoma and all secondary growths. In the unverified group no case was included in which there was reasonable doubt of the diagnosis. It is necessary to consider all cases seen if a true picture of operability and over-all salvage rates is to be obtained.

The sex incidence in this series parallels that in other reported groups. Of the verified cases, 85.8 per cent were in males and 14.2 per cent in females.

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It has been our practice to advise surgical exploration in all suspected or proved cases with but

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Exploration only	127	15 (11.8 %)
Resection	162	29 (17.9 %)
Without extrapulmonary extension	55	
Microscopical extension only	49	
Gross extension	58	
Totals	289	44 (15.2 %)

*Of these, 481 were verified.

two exceptions: absolute or strong presumptive evidence that the growth is out of bounds, and cases in which the patient's general condition is too poor.

TABLE 2 Data in 234 Cases of Primary Carcinoma of the Lung (1932-1948)*

OPERATION	NO. OF CASES	NO. OF DEATHS†
Exploration	58	9 (15.5 %)
Resection	41	9 (21.9 %)
Without extrapulmonary extension	20	
Lymph node extension only	10	
Gross extension	11	
Totals	99	18 (18.1 %)

*Of these, 190 were verified.

†The five-year survival (4.3 per cent of all cases seen and 5.3 per cent of all verified cases) was distributed as follows: 8 cases without extrapulmonary extension and 2 cases with lymph node extension only.

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*Presented at the annual meeting of the New England Surgical Society, New Haven, Connecticut, October 1, 1948.

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Figure 1 shows the survival periods of all patients who submitted to pulmonary resection. It will be seen that of the patients operated upon within the past year, 60 per cent are still alive with 8 late deaths and 8 operative deaths. Of those operated upon five years or more ago, 24.4 per cent are still alive (10 patients).

An analysis of the survival periods in the cases without extension is shown in Figure 2. It will be seen that of 11 patients operated upon in the past year, there was 1 operative death, and all the rest are still living. Sixteen patients are living more than a year, 14 more than two years, 12 more than three years, 9 more than four years, and 8 more than five years after operation.

If operative deaths are excluded, 10 patients, or 100 per cent of those who survived operation within the past year, are still living, whereas 8 (50 per cent)

in which a palliative resection was done — that is, one in which gross tumor tissue was left behind. In the remaining 24 cases, gross extension was encountered, but all detectable tumor tissue was removed. This group includes the following cases in which there was invasion of the ribs or chest wall, cases in which there was mediastinal invasion, including those in which there was invasion of the pericardium, and cases in which there was invasion of the diaphragm. In all, the invasion was apparent on gross examination, as distinguished from the lymphatic metastases of the preceding group.

Of 43 patients in this category operated upon more than a year ago, only 1 is alive. This man has an epidermoid carcinoma (Grade II) and has lived

TABLE 3 Survival Periods from Diagnosis to Death from Disease in Cases of Primary Carcinoma of the Lung

TREATMENT	NO. OF CASES	SURVIVAL
None	148	4.4
Exploration	102	7.0
Resection		
Gross extension	35	10.0
Lymph nodes involved	22	9.6
No apparent extension	19	11.1

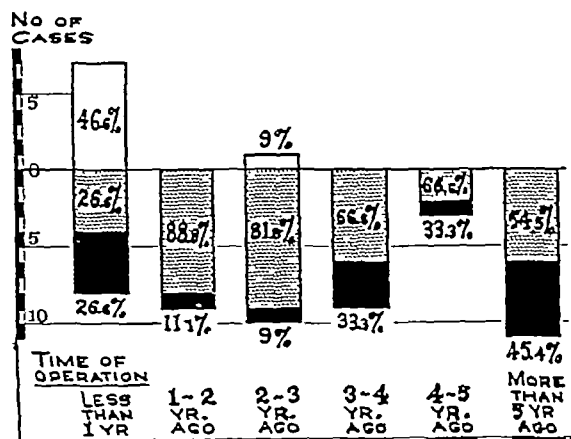


FIGURE 4 Survival after Resection in 50 Cases with Gross Extension

of those who survived operation five or more years ago are still alive.

The average duration of life of those who died postoperatively (excluding hospital deaths) was eleven and one-tenth months. Of these, none lived longer than twenty-eight months.

Cases in which there was lymph-node extension only are shown in Figure 3. In the majority of these cases the lymph nodes were found to be involved as a result of microscopical study, but in the few cases in which the glands were grossly involved, all tumor tissue was thought to have been removed. As can be seen from the chart, 8 of 28 patients are alive more than two years and 2 of 10 are alive five years or more after operation. Of the late deaths, the average duration of life was nine and three-fifths months. Of these, no patient lived longer than twenty-three months.

The group in which there was gross extension is shown in Figure 4. There were 34 cases in this group

more than two years. His was a palliative resection in which gross tumor was left behind, so that there is no possibility of cure. All the other 7 survivors were operated upon less than a year ago. In this group, the average life of those who died postoperatively was ten months, excluding hospital deaths. The longest survivor lived twenty-nine months. This experience indicates that the prognosis is poor if gross extension has occurred, even if all detectable tumor is removed. We have been agreeably surprised at the number of survivors in the group with lymph-node extension. Other reports from the literature bearing upon this subject are few. Ochsner, DeBakey and Dixon⁷ reported that in their series of cases with either lymph-node or gross extension only 2 of 27 patients in this combined group survived beyond a three-year period, and none beyond six years. Coleman¹⁰ reported the cures of 2 patients still living two and six years respectively after resection in which the tumor had invaded the ribs. In our own series there were 6 cases, but no patient has survived more than twenty-seven months.

SURVIVAL IN RELATION TO TYPE OF PROCEDURE

The vast majority of patients in our resection series have been treated by pneumonectomy. Only by mass removal of the lung can all hilar lymph nodes be resected, and mediastinal dissection is

Of all cases, 48 per cent were explored, and resection was carried out in 27 per cent. In recent years, there has been an encouraging trend toward higher rates of operability, and in the past five years, 51 per cent of all cases seen have been explored and 32 per cent resected.

In Table 1 and 2 and Figure 2, 3 and 4 the resections are divided into three categories according to the extent of the lesion: patients with no demon-

strated extension, patients in whom all tumor was thought to have been removed (candidates for cure if all tumor is re-

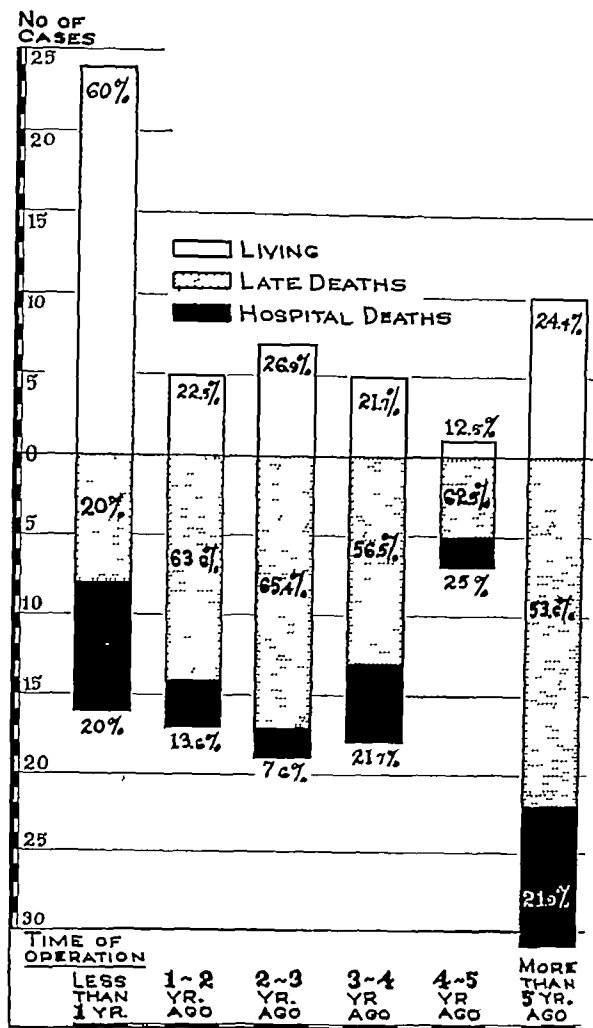


FIGURE 1 Survival in Total of 162 Patients who Submitted to Resection

There were 29 operative deaths, 2 patients who could not be followed, 3 who died of causes other than recurrent cancer, and 2 epidermoid carcinomas that were not graded (leaving a total of 126 cases, which are considered in the succeeding figures)

strable extrapulmonary extension (these are the best candidates for cure), those with lymph-node metastases only, the regional lymph nodes being grossly involved in some and the metastases being found on microscopical examination in others (candidates for possible cure if the excised nodes represented the sole metastatic process), and those with gross evidence of extension, in turn divided into pa-

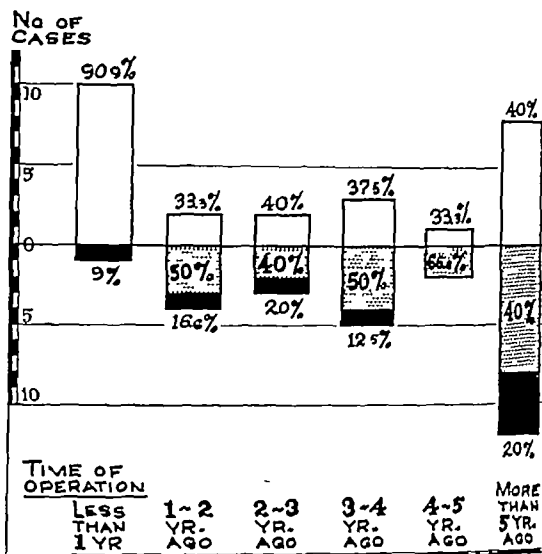


FIGURE 2 Survival after Resection in 56 Cases without Extension

moved) and those in whom gross tumor was left behind (palliative procedure only)

SURVIVAL PERIODS

The survival periods of patients who were known to have died from their disease are shown in Table 3

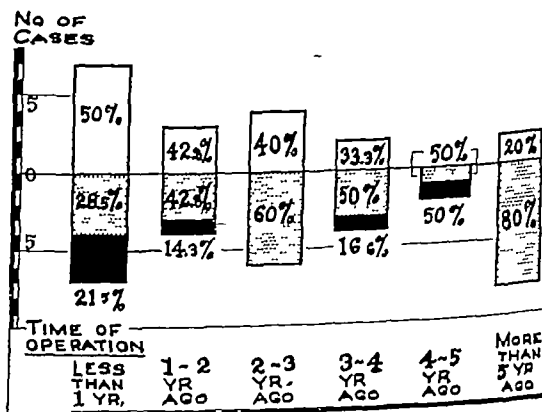


FIGURE 3 Survival after Resection in 49 Cases with Lymph Node Extension Only

In cases in which the cancer was obviously out of bounds and in which no surgical treatment was offered the patients lived an average of four and two-fifths months. At the other end was a group of 19 patients submitted to resection in whom the growth apparently was localized but who subsequently died of their disease. The average survival of this group was eleven and three-tenths months.

without apparent extension of any kind. The patients surviving for three and two years both had lymph-node metastases. Of those who died, 4 had gross extension, and 2 had lymph-node metastases, the average survival was fifteen and one-tenth

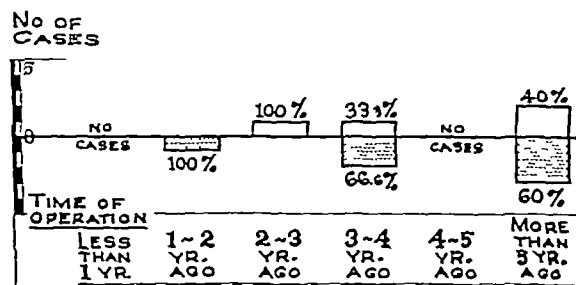


FIGURE 8 Survival after Resection in 10 Cases of Epidermoid Carcinoma (Grade I)

months, and yet no patient lived more than twenty-seven months.

In the cases of epidermoid carcinoma (Grade II) there were 36 patients, of whom 20 still survive, 8 of 18 having lived longer than three years, and 5 of 10 having lived longer than five years (Fig 9). In 3 of 5 cases in which there was no extension of

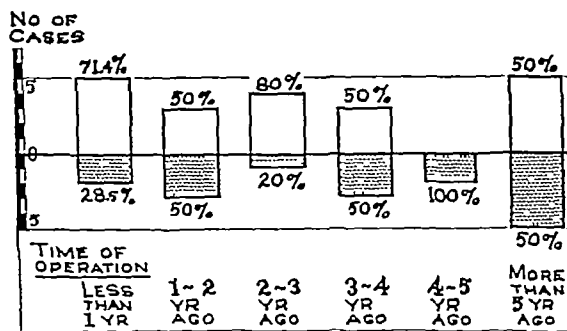


FIGURE 9 Survival after Resection in 36 Cases of Epidermoid Carcinoma (Grade II)

the tumor the patients have survived five years or more after operation, and 5 of 9 patients in this same group have survived three years or more. Two of 5 patients with lymph-node metastases are still living five years or more, and 3 of 8 cases are living three years or more after operation. No patient who died lived longer than twenty-four months, and the average survival was twelve and nine-tenths months.

Of 33 cases in the group diagnosed epidermoid carcinoma (Grade III), 3 of 6 patients operated upon five years or more ago and 4 of 8 operated upon more than four years ago still survive (Fig 10). However, there are no survivors among the patients operated on three, two and one years

ago. Of those operated upon more than four years ago, the 4 survivors were in the group without extension of the tumor. In the intervening years, however, 3 other patients without extension have died. Four patients with lymph-node extension upon whom operation was performed more than a year ago have all died, as have 6 with gross extension. The average duration of life in the late deaths was eight and two-fifths months, and no patient lived longer than twenty-eight months.

SYMPTOMS AND SURVIVAL

All patients submitted to resection were divided into three groups: those who had symptoms for less

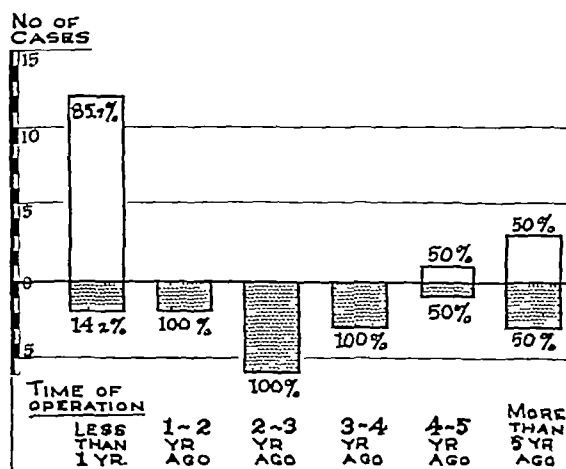


FIGURE 10 Survival after Resection in 33 Cases of Epidermoid Carcinoma (Grade III)

than six months, those with symptoms for six to twelve months, and those with symptoms for more than a year. One would expect to find a higher number of survivors in those patients who had symptoms for less than six months, and yet it was found that in this group the percentage of survivors was lower than that in patients who had symptoms for six to twelve months. The percentage of survivors of those who had symptoms for more than a year was about the same as that in patients who had symptoms for less than six months. This finding could be interpreted to mean that many growths are relatively far advanced by the time symptoms develop. No attempt was made, however, to correlate pathology with the duration of symptoms. Many patients with anaplastic tumors presented themselves before they had had symptoms for a year, whereas others with more slowly growing tumors waited longer before consulting a physician.

Those patients who survived for more than five years are shown in Table 4. All were treated by total pneumonectomy. Of these, 5 are well, 2 are reasonably well, and the last available information concerning another revealed that she was well in

facilitated. Occasionally, however, in a patient of advanced age or one with a narrow respiratory reserve who has a peripheral tumor, lobectomy may be preferable. This is particularly true if there is positive evidence of gross extrapulmonary extension. Palliative lobectomy was performed upon a few patients who had peripheral tumors with invasion of the chest wall that could not be totally resected. However, it has been found that these procedures are rarely satisfactory in relieving pain even if coupled with division of the intercostal nerves. Treatment by rhizotomy, high chordotomy or frontal lobotomy if the pain is severe should receive consideration. Lobectomy was performed on 8 patients in our series, 4 of whom were operated upon more than two years ago, and all these are dead. Four patients treated by lobectomy within the past two years are still living.

PATHOLOGY IN RELATION TO SURVIVAL

The pathological cell type is second only to the extension of the tumor in determining survival. The pathologist has divided all the pathologic cell types into three major classifications: undifferentiated carcinoma, carcinoma arising from glandular epithelium, including adenocarcinoma and carcinoma

with lymph-node metastases only, and 2 with gross extension. The surviving patient had no demonstrable extension at the time of operation. The average duration of life of those who died was ten and two-tenths months, and of this group, none lived longer than twenty-seven months.

There were 10 cases in which carcinoma simplex was diagnosed (Fig 7). None of the patients

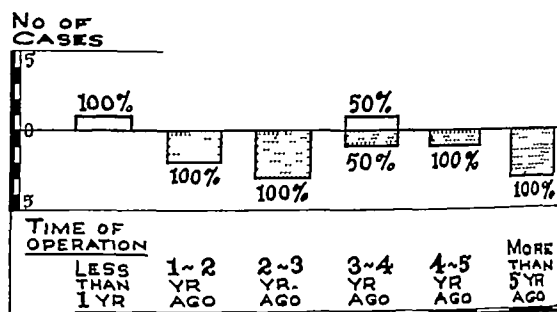


FIGURE 6 Survival after Resection in 12 Cases of Adenocarcinoma

operated upon more than a year ago are still alive. Only 1 of 3 patients operated upon within the past year is still alive. In this entire group, there were 3 cases in which there was no apparent extension, 4 in which there was lymph-node metastasis only, and 3 in which there was gross extension. The average

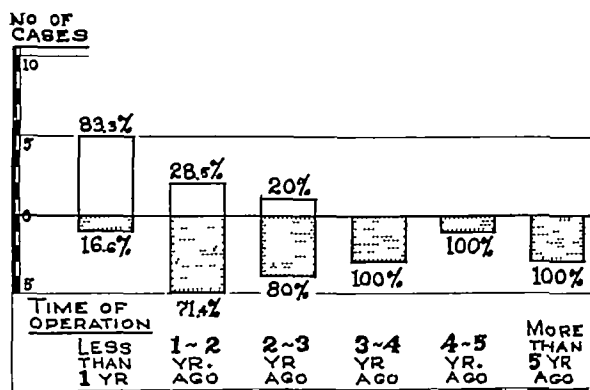


FIGURE 5 Survival after Resection in 25 Cases of Undifferentiated Carcinoma

simplex, and epidermoid carcinoma, including sub-groupings Grades I, II and III.

Only those who survived operation are considered.

In the undifferentiated group (Fig 5), there were 25 cases. There was no apparent extension of the tumor in 4 of the 7 patients operated upon more than three years ago, and yet none are living. In the late deaths, no patient lived longer than twenty-nine months, and the average duration of life of those who died was nine and three-tenths months.

In the adenocarcinoma group (Fig 6), there were 12 cases. Of the 6 patients upon whom operation was performed more than three years previously, it will be seen that only 1 patient has survived. In this group of 6 cases, there were 3 without extension, 1

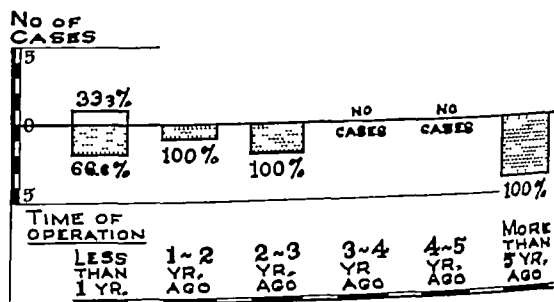


FIGURE 7 Survival after Resection in 10 Cases of Carcinoma Simplex

duration of life of patients who died was seven and three-tenths months, and none lived longer than thirteen months.

The final group to be considered in relation to survival to pathological type is that in which the diagnosis was epidermoid carcinoma, and it is in these cases that the prognosis is most favorable.

In cases diagnosed as Grade I (Fig 8) there were 10 cases. It will be seen that 4 of these patients are still living more than two years, 3 of 8 patients more than three years, and 2 of 5 patients living more than five years after operation. The 2 patients living more than five years after operation were both in the group

bronchoscopy or even exploratory thoracotomy may be necessary to settle the diagnosis

Efforts to discover primary carcinoma of the lung in its silent and early stage will be rewarded. The risk of resection is reasonably low and is constantly being lowered. Five-year survival rates for patients treated at a time when the growth was apparently localized have been high

SUMMARY

Statistics bearing upon operability and survival of 604 patients in whom the diagnosis of primary carcinoma of the lung was made are presented

The extension or localization of the lesion and the pathological cell type are the most important factors in survival after resection

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bronchial tumor. One patient has not been followed. Ten of the remaining 25 patients have lived five to fifteen and a half years after operation. In the adenoma series, there were no operative deaths; therefore, since immediate and late results are so totally different in the "so-called" adenoma group, we have not included them in the above paper on true cancer of the lung

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PULMONARY EMBOLISM*

Analysis of 74 Autopsy Cases Since 1941

KLAUS DEHLINGER, M D,† AND PAUL RIEMENSCHNEIDER, M D‡

BOSTON

THERE has been no significant decrease in the percentage of cases in which pulmonary emboli were demonstrated at autopsy at this hospital group since the introduction of definitive and prophylactic treatment of venous thrombosis. This therapy includes venous interruption and the administration of heparin and dicumarol, as well as prophylactic exercises, early ambulation and even paravertebral autonomic block in one case. During the thirteen years from 1928 through 1940 pulmonary emboli were found in 7.5 per cent of all autopsies, whereas the figure became 6.7 per cent during the following six-year period (Table 1). The percentage of operations that were followed by pulmonary embolism, as found at post-mortem examination, has decreased somewhat more in the same intervals. Before January, 1941, the figure was 0.13 per cent, since that date it has dropped to 0.09

per cent, but even this decrease is not definitely significant statistically. ‡

Because there are so many factors that may change over a period of years, making statistical data questionable, Table 2 was compiled. It shows the various relations between the number of hospital admissions, operations, deaths, autopsies and pulmonary-embolism autopsies per year since 1928. The ratio of operations to hospital admissions has gradually increased over the years. We feel safe in concluding that the other individual ratios have not changed enough to make the above percentages on pulmonary embolism at autopsy lose their significance.

*The standard error of the difference for the percentages was calculated according to the formula given in Arkin and Cotton.¹ The actual difference between the two figures (7.475-6.655=0.790) is only 0.22 times the standard error of the difference (3.534). This is definitely not significant, for the chances are more than eight out of ten that the actual difference is an accidental one.
Using the same formula for the percentage of operations followed by embolism as that found at autopsy for the same groups of years, we find that the actual difference between the two (0.0412 per cent) is 2.5 times the standard error of the difference (0.0177 per cent) which may be significant.

*From the Laboratory of Pathology of the New England Deaconess and New England Baptist hospitals.
†Resident in radiology, Peter Bent Brigham Hospital formerly assistant resident in pathology, New England Deaconess Hospital.

1947 Of the 2 remaining patients, 1 was well for ten years but has gone downhill in the past two years and is now a respiratory invalid, the other was well for five years and has had a similar downhill course in the past two years. Both are apparently free of cancer but are suffering from a lack of respiratory reserve.

In the group of patients operated upon more than five years ago, there is an additional patient who died in an accident thirty-nine months after resection. He was working every day until his death, and was apparently free of disease. He pre-

histories of patients seen in 1947 and 1948 showed that the interval between the first symptom and the date of diagnosis had been reduced only to ten months. The average patient delayed seeing a doctor for three and eight-tenths months. The first x-ray film was ordered one and six-tenths months later, compared with an interval of three months in the earlier group. However, the diagnosis was not established until four and six-tenths months later.

The interval between onset of symptoms and diagnosis will have to be shortened, in fact, this

TABLE 4 *Results in Patients Who Have Survived Five or More Years after Pulmonary Resection for Carcinoma of the Lung*

CASE NO	DATE OF OPERATION	AGE	SEX	FINAL DIAGNOSIS	PRESENT STATUS
1	3/13/36	yr 45	M	Epidermoid carcinoma (Grade II)	Patient well for 10 years downhill in past 2 years, now respiratory invalid.
2	6/10/37	45	F	Epidermoid carcinoma (Grade III)	According to last information (1947) patient well
3	3/18/41	44	M	Epidermoid carcinoma (Grade III)	Patient well for 5 years downhill in past 2 years now respiratory invalid.
4	10/11/41	43	M	Epidermoid carcinoma (Grade I)	Patient well does light work some dyspnea upon exertion only
5	5/7/42	36	M	Epidermoid carcinoma (Grade II)	Patient well
6	4/16/42	48	M	Epidermoid carcinoma (Grade II)	Patient well works every day some dyspnea upon exertion only
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sumably had been cured, for in our entire series no patient who later died of his disease has lived longer than thirty months after diagnosis. This includes untreated patients, those in whom thoracotomy only was performed, and those who had pulmonary resection. All who died had signs and symptoms of cancer for several months prior to death, so that it appears from our experience that any patient who lives thirty months or more without symptoms of recurrence has an excellent chance for cure.

FUTURE POSSIBILITIES

The present method of waiting for symptoms, followed by the delay that seems to be necessary to work out the differential diagnosis, has not produced the results that we believe are possible in the present-day surgical treatment of primary carcinoma of the lung.

It was previously pointed out that an analysis of the histories of 133 patients seen between 1932 and 1942 revealed that there was an average interval of eleven and three-fourths months between the first symptom and the establishment of the diagnosis.¹¹ The average patient delayed seeing a doctor for three months. The first x-ray examination was not ordered until another three months had elapsed. The diagnosis was established five and three-fourths months later. A review of the

interval can be eliminated altogether. The growth can be discovered before it is large enough to produce symptoms. Radiologic screening of the population, now being employed in uncovering cases of silent tuberculosis, can be further extended. Older age groups should be included, and the screening should be repeated each year. Early carcinomas usually produce changes in the x-ray picture that can be detected by the experienced observer, even if the tumor itself will not cast a shadow. Approximately 80 per cent of the lesions are situated in a lobar or segmental bronchus, and the secondary changes in the corresponding segment or lobe, incident to partial or total bronchial occlusion, cast abnormal shadows detectable in the miniature film used for screening. There is a period during the growth of the tumor when abnormal x-ray densities develop and then symptoms appear. Part of this period of silent growth can be saved. The minority group of peripheral tumors cast direct shadows, which, even in their early stages, should be caught in the screening process owing to the highly rarefied normal lung field. If abnormal densities are discovered, they will require proper identification without delay. Additional x-ray studies should be arranged for immediately. Cytologic examination of the sputum and of material aspirated from the bronchi (Papanicolaou technic),

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embolism as the primary cause of death to be ten and a third years older than the average age of the patient at operation

The immediate cause of death in these cases has changed somewhat through the years. In the recent six-year group of 74 cases, embolism was considered the immediate cause in 58. The other causes were as follows: cardiac infarction 3, cardiac failure 3, pulmonary insufficiency 2, pulmonary edema 1, sepsis 2, peritonitis 1, and undetermined 4 cases. It will be noted that only 3 were ascribed to infection. Again, with the first 74 cases since 1928 for

patient who lived only thirty-three hours post-operatively had no recognized symptoms of thrombosis before the surgical procedure. These time relations are in accord with other data in the literature, which include many more cases and have been reviewed by Neuhof and Klein.²

Conclusions regarding the primary sites of the thrombi have been divergent in the literature. Some claim that almost all thrombi arise in the tributaries of the common femoral vein. On the other hand, Moran⁹ found that 45 per cent of all male patients who died with pulmonary emboli had prostatic

TABLE 3 Comparison of Recent and Remote Autopsied Cases of Pulmonary Embolism

PERIOD	ARITHMETIC MEAN AGE	DEATHS DIRECTLY ATTRIBUTABLE TO EMBOLISM	DEATHS DIRECTLY ATTRIBUTABLE TO INFECTION	PATIENTS OPERATED ON	PATIENTS NOT OPERATED ON
1941-1946 (74 cases)	57	58	3	53	21
1928-1940 (74 cases)	60.0	48	11	50	24

comparison (Table 3) pulmonary embolism was considered the immediate cause of death in 48, whereas infection accounted for 11. Because infection is now controllable to a great extent, embolism as the immediate cause of death has become in recent years relatively more rather than less common in this series.

The role of surgery as a causative factor in thromboembolic disease is difficult to evaluate. In the early literature it was especially stressed, but more recently it has been shown that a greater percentage of medical patients than of those subjected to surgery die of pulmonary embolism.^{6,7} In the recent series, 72 per cent (53 patients) underwent operations. This is approximately the percentage of surgical cases in this group of hospitals. It is, however, the group of 21 patients not operated upon that are especially worthy of consideration. Only 5 had mural thrombi in the heart, 2 of these also had leg thrombi. Thus, 16 to 18 of 21 patients who were not operated on died with pulmonary emboli originating from veins rather than from the endocardium. These figures substantiate the views of Hunter et al.⁸ that the common denominator of hospitalized medical and surgical patients is confinement to bed irrespective of the type of disease, and that therefore recumbency is probably the greatest single factor in thrombus formation.

The duration of bed rest in this group cannot be determined, for it is not known how long the patients had been in bed before entering the hospital or undergoing surgery. However, the interval from operation to death in patients who underwent a single recent operation is known (Fig 1). The time extremes are thirty-three hours and thirty-six days, with an arithmetic mean of twelve days. The

thrombi. In 96 patients who died because of a massive embolus Cohn and Walsh¹⁰ found thrombi in 31 of the femoral or iliac veins, 20 in the pelvic veins (14 periprostatic), 4 in the tributaries of the superior vena cava and 7 in the right side of the heart, and in 37 no thrombus was found. Our figures were similar. In reviewing these figures one must keep in mind that with a changing resident staff in

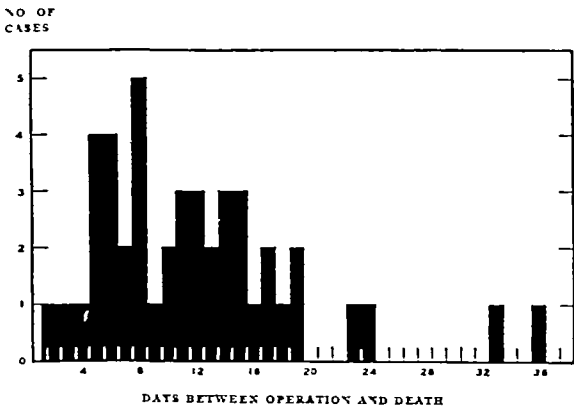


FIGURE 1 Interval between Operation and Death in Patients Undergoing a Single Operation

pathology the interest in this problem has waxed and waned so that the primary site of thrombus was searched for with varying degrees of diligence. In Neuhof's² series, for example, no primary thrombus was found in over 50 per cent of the cases.

We classified the primary sites of thrombi into three groups according to the probable value of interruption of the common femoral vein (Fig 2). The procedure was considered helpful, valueless or questionably helpful (Table 4). The first group

The purpose of this study is to attempt to determine why many patients are still dying with pulmonary embolism despite the availability of anticoagulant drugs and the general use of venous interruption in recent years. No analysis of the numerous successfully treated cases was made. Hence this report should not be considered in any

ing data can be obtained. Some of these cases have been previously reported in a different type of study by Evans.⁴

There were 41 men and 33 women. Most authors on the subject agree that there is no sex difference, except possibly that the pelvic venous plexuses are more often disturbed surgically in the female, and

TABLE 1 *Relations of Pulmonary Embolism at Autopsy to Total Number of Autopsies and Operations*

PERIOD	NO OF AUTOPSIES	NO OF AUTOPSIES WITH PULMONARY EMBOLISM	PERCENTAGE OF AUTOPSIES WITH PULMONARY EMBOLISM	NO OF OPERATIONS	NO OF OPERATED CASES WITH PULMONARY EMBOLISM AT AUTOPSY	PERCENTAGE OF OPERATIONS WITH PULMONARY EMBOLISM AT AUTOPSY
1928-1940	2366	177	7.5	88 622	115	0.13
1941-1946	1107	74	6.7	59 894	53	0.09

sense a condemnation of the methods in use at the present time for the prevention of pulmonary embolism, but rather an indication that the problem is still great even though some of the recent papers lead one to believe that it has been all but completely solved. No attempt has been made to review the literature because this has been

that this sex group might therefore be more frequently affected.²⁻⁵ Ages varied from twenty-four to eighty-six years, with an arithmetic mean of sixty years. One might argue that we have not seen a greater decrease in thromboembolic deaths because an older age group has been operated upon in recent years, however, the arithmetic mean of

TABLE 2 *Annual Breakdown of Statistics Concerning Total Number of Deaths, Autopsies, Operations and Pulmonary Embolism*

YEAR	ADMISSIONS	OPERATIONS	DEATHS	AUTOPSIES	CASES OF PULMONARY EMBOLISM AT AUTOPSY	OPERATED CASES WITH PULMONARY EMBOLISM AT AUTOPSY	RATIO OF OPERATIONS TO ADMISSIONS	PERCENTAGE OF FATAL CASES OF PULMONARY EMBOLISM AT AUTOPSY	PERCENTAGE OF AUTOPSIES WITH PULMONARY EMBOLISM	PERCENTAGE OF OPERATIONS FOLLOWED BY PULMONARY EMBOLISM AS FOUND AT AUTOPSY
1928	7,796	4,358	225	181	10	5	0.56	60.0	5.5	0.11
1929	9,601	4,619	266	206	20	13	0.48	77.0	9.7	0.28
1930	9,604	5,554	252	178	15	8	0.57	72.0	8.4	0.14
1931	9,856	5,752	237	154	6	4	0.58	65.0	3.9	0.07
1932	9,137	5,352	231	143	7	5	0.59	61.0	4.9	0.09
1933	9,026	5,523	252	154	10	7	0.61	61.0	6.5	0.13
1934	10,743	6,574	306	201	17	13	0.61	66.0	8.5	0.20
1935	10,578	6,757	305	181	16	6	0.64	59.0	8.8	0.09
1936	12,257	7,804	319	197	23	18	0.64	62.0	11.7	0.23
1937	12,987	8,725	350	199	7	5	0.67	57.0	3.3	0.05
1938	12,988	8,843	389	213	13	13	0.68	55.0	8.5	0.15
1939	13,399	9,128	339	187	16	8	0.68	55.0	8.6	0.09
1940	13,313	9,651	350	172	12	10	0.72	49.0	7.0	0.10
Totals	141 485	88 640	3 821	2 366	177	115				
Averages							0.63	62.0	7.47	0.150
1941	13,542	9,355	311	172	10	6	0.69	55.0	5.8	0.06
1942	13,931	9,837	329	172	15	10	0.71	52.0	8.7	0.10
1943	12,956	9,909	358	214	8	6	0.76	60.0	3.7	0.06
1944	12,245	10,368	299	172	10	8	0.85	51.0	5.8	0.03
1945	11,610	9,935	317	200	14	11	0.86	63.0	7.0	0.11
1946	11,932	10,450	315	177	17	12	0.88	56.0	9.0	0.11
Totals	76 216	59 894	1 929	1 107	74	53				
Averages							0.79	57.0	6.63	0.059
Grand totals	217 701	148 534	5 750	3 473	251	163				
Averages							0.68	60.4	7.23	0.113

excellently done by Neuhof and Klein² and Homans.³

Seventy-four consecutive autopsy cases with pulmonary embolism in the six-year period from 1941 through 1946 have been studied. Breakdown of so small a number of cases cannot be expected to give statistically significant results, but interest-

the ages for the first 74 autopsied cases with pulmonary embolism since 1928 was found to be slightly over fifty-eight years. Thus, there is even less than twenty-four months' difference between the average ages of the two groups. It is of interest that Henderson⁵ found the average age in 223 patients dying after operation with pulmonary

monary infarction was the sole pathologic finding in the lungs at autopsy. Chest roentgenograms of 5 of these showed no abnormal densities in the lung fields, so that in all probability the emboli lodged in the pulmonary arteries after the film was taken. In the remaining 5 cases, the greatest misinterpretation of shadows cast by lung infarcts as the only pathologic process found at autopsy was the diagnosis of pneumonitis or bronchopneumonia (4 cases).

Since 1941 the clinicians at this group of hospitals have been actively treating patients to prevent pulmonary emboli. The Lahey Clinic alone treated 184 postoperative cases of venous thrombosis with or without pulmonary embolism from 1942 through 1946. In these only 3 patients died of thromboembolic disease.¹¹ Yet the most surprising result of our study was that in the 74 autopsied cases only 5 patients had received any definitive treatment to prevent embolism. This emphasizes the difficulty in recognizing venous thrombosis and benign pulmonary embolism. Three of these patients died with embolism as the immediate cause of death. The other 2 died of unrelated conditions, and the minor emboli were incidental findings.

Thus, despite the many enthusiastic reports on venous interruption and anticoagulant therapy for the prevention of pulmonary embolism, the problem is still far from solved, and the careful search for the slightest symptoms suggestive of venous thrombosis and pulmonary embolism remains a most important responsibility of every physician.

SUMMARY

The incidence of autopsied cases with demonstrable pulmonary embolism has dropped only from 7.5 to 6.7 per cent since the use of definitive and prophylactic treatment of venous thrombosis, including venous interruption and the administration of heparin and dicumarol.

The decrease is slightly greater when the percentage of deaths coming to autopsy with pulmonary

emboli is compared to the number of operations performed, rather than to the total number of autopsies done. From 1928 through 1940 it was 0.13 per cent, whereas from 1941 through 1946 it was 0.09 per cent. From a statistical standpoint this might be a significant decrease.

A study of the 74 cases autopsied from 1941 through 1946 was undertaken to help explain this relatively insignificant change. The cases were analyzed according to age, sex, immediate cause of death, primary site of thrombus, medical versus surgical status and preventive therapy.

In only 5 of the 74 autopsied cases of pulmonary emboli did the patients receive specific therapy for the prevention of embolism. This suggests that the primary problem is the difficulty in the diagnosis of venous thrombosis and nonfatal pulmonary embolism.

Despite the availability of various means of preventing pulmonary embolism, the condition remains a great problem.

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comprises 15 cases in which femoral-vein ligation was considered helpful, in each, a thrombus was found in the veins below the inguinal ligament. The second group consists of 15 cases in which

cases in which the procedure might have been helpful if it had been performed early enough, it includes the cases in which a thrombus was found in the veins collecting blood from the femoral vein but was proximal to the inguinal ligament—namely, the external iliac, common iliac and inferior vena cava—as well as the 25 cases in which no primary thrombus was found. These figures lead us to conclude that interruption of the common femoral vein is not the ideal approach to the prevention of embolic phenomena.

The greatest problem of all, however, is still the difficulty in recognizing venous thrombosis and benign pulmonary embolism before further embolism results in death. In many of the charts in these 74 cases no evidence of venous thrombosis was given, except possibly a slight rise in pulse and temperature. In other cases, however, the patient had chest symptoms that were diagnosed as pneumonitis, pulmonary edema, atelectasis and coronary thrombosis and remained unrecognized as embolic episodes until death. Evans⁴ found in retrospect that 85 per cent of 52 postoperative fatal cases had premonitory signs and symptoms for a sufficiently long time before fatal embolism to have allowed adequate therapy to have been administered.

Roentgenograms are not so helpful as one might think. In only 28 of the 74 fatal cases were there sufficient chest symptoms during the last week of life before the final agonal episode to warrant x-ray examination of the chest. In 18 of these 28 cases pulmonary embolism was not recognized radiographically because of additional coexistent pulmonary and pleural abnormalities as shown by autopsy. These included pulmonary cancer in 4 cases, pulmonary congestion in 3, pneumonitis in 2, and atelectasis, pneumonitis and atelectasis, lung

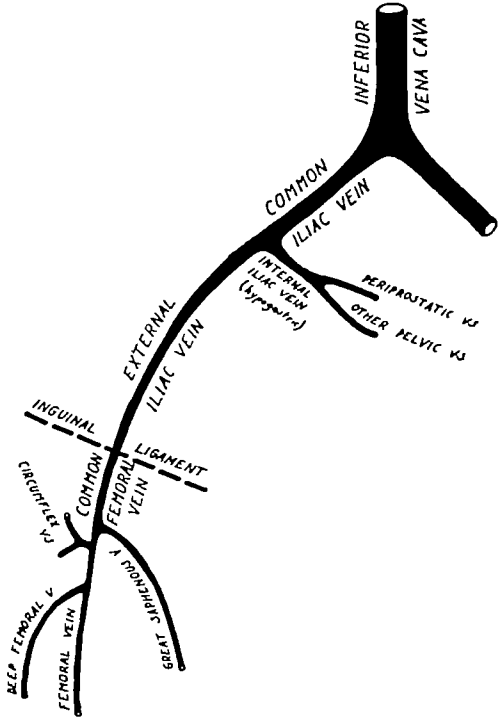


FIGURE 2 Simplified Diagram, Showing Venous Return from the Leg and Pelvis

femoral-vein interruption would have been valueless because the primary thrombus was either in the tributaries of the hypogastric vein or on the

TABLE 4 Potential Value of Common-Femoral-Vein Interruption according to Site of Primary Thrombus

SITE OF THROMBUS	OPERATED CASES	NONOPERATED CASES	TOTALS
Interruption helpful			
Common femoral vein or tributaries or both	12	3	15
Interruption valueless			
Hypogastric vein or tributaries or both	5	2	7
Both external iliac and hypogastric veins or tributaries or both	2	0	2
Right side of heart and inferior vena cava tributaries	1	2	3
Right auricle or ventricle or both	0	3	3
Interruption questionably helpful			
External iliac vein with or without its tributaries	1	0	1
Common iliac vein or inferior vena cava or both	8	5	11
Questionable (leg symptoms without autopsy confirmation)	5	1	6
Questionable (arm symptoms without autopsy confirmation)	1	0	1
Undetermined	18	7	25
Totals	53	21	74

endocardium of the right side of the heart, fatal pulmonary emboli could probably have been prevented in 9 of these by tying off of the inferior vena cava. The third group contains the remaining 44

abscess, chronic empyema, fibrous pleural adhesions and effusion with pneumothorax in 1 each. This leaves only 10 cases with x-ray films available in which pulmonary embolism with or without pul-

of 9 millimols per liter and a serum potassium of 4.43 milliequiv per liter. Treatment, which was immediately instituted, consisted of 3 liters of physiologic saline solution and 450 units of regular insulin. The lowest serum potassium, which was determined 20 hours after admission, was 3.6 milliequiv per liter.

CASE 5 A young adult in mild acidosis had a carbon dioxide content of 10 millimols per liter and a blood sugar of 296 mg per 100 cc. This patient required only 165 units of regular insulin, and the serum potassium fell from a normal of 4.3 to only 4.1 milliequiv per liter.

CASE 6 An elderly woman with known diabetes who had never required insulin was found comatose in her apartment after approximately 24 hours of acidosis. After hospitalization and institution of treatment she responded to 340 units of insulin and roused from her coma. She continued anuric, however, and suddenly vomited and aspirated a large amount of material in spite of previous gastric lavage. Death was due to asphyxia.

DISCUSSION

The cause of low serum potassium levels may be contrasted with those of high values, which occur almost without exception in patients with oliguria

on admission. The period of early recovery from coma may indeed be one of the most dangerous periods from a chemical standpoint. Thus, the serum potassium levels in Cases 2 and 6, which were slightly elevated on admission, fell to below the normal range in a period of four to twenty-four hours after recovery from coma. This factor makes imperative the early feeding by mouth of orange juice and other foods rich in potassium.

Various aspects of emergency serum potassium levels in diabetic coma are presented in Table 2. The diagnosis of low serum potassium is particularly to be borne in mind when a patient in diabetic coma has received glucose solution by vein early, and, at a period varying from four to twenty-four hours after the beginning of treatment, shows the characteristic clinical signs. So far, no patient in this series (or in other reports from the literature) who has not received considerable amounts of glu-

TABLE 2 *Emergency Serum Potassium Levels in Diabetic Coma*

POTASSIUM LEVEL	CAUSES	DIAGNOSTIC FEATURES	TREATMENT	PREVENTION
Low	Insufficient or delayed treatment of acidosis; extreme diuresis with loss of potassium in urine; excessive administration of glucose, with glycogen deposition vomiting	Sudden flaccid paralysis progressing to respiratory paralysis 10-24 hr after treatment with glucose and insulin; fish mouth facial expression; low-voltage QRS complexes and flat or inverted T waves fall in serum potassium from normal of 4.1 to 5.6 milliequiv per liter to less than 3.0 milliequiv	Potassium phosphate (2 gm.) with potassium dihydrogen phosphate (0.4 gm.) intravenously 100 cc of 2 per cent potassium chloride solution intravenously	Withholding of glucose from patients in coma; rapid treatment to shorten acidosis; early feeding of potassium-containing food (oatmeal, orange juice and so forth)
High	Oliguria or anuria; administration of potassium in acute or chronic renal failure	Paralysis (flaccid) or spastic type; absent P waves; wide QRS complexes and high peaked T waves; high value for serum potassium (levels exceeding 12 milliequiv per liter may be fatal)	Cause should be treated; administration of glucose and insulin	No administration of potassium (without sure indication)

or anuria. Cases 2 and 6 in this series illustrate this point well. Each patient was anuric for a variable period before treatment, and in each, the admission potassium level was slightly above normal limits. As early as 1915, Smillie⁶ described potassium poisoning in nephritis when potassium salts were administered therapeutically. Van Slyke⁷ points out that a fall in systolic blood pressure of 40 to 60 may in itself be sufficient to cause anuria. Such levels are not at all rare in severe diabetic coma. It should be recalled, however, that elevated serum potassium levels in diabetic acidosis and shock do not necessarily reflect the true state of the tissue cells of the body. Prior to the late stage of anuria and hemoconcentration, there is usually a prolonged period of diuresis with resultant potassium loss. Thus, the ambiguous condition results in which there is a total body deficit of potassium in the presence of an elevated serum potassium level. This condition must be borne in mind during treatment, and a false sense of security avoided when one finds a normal or slightly elevated level

during the first few hours of treatment has shown seriously low serum potassium levels. The actual diagnosis is, of course, best established by serial analyses of the serum. Since this determination is not always obtainable, however, one should always remember that (in patients with low serum potassium levels) the sudden development of marked muscular weakness or actual flaccid paralysis may mean hypopotassemia. In 1 or 2 patients a peculiar fish-mouth facial expression has been noted. An important diagnostic aid is afforded by the electrocardiogram, in which the changes accompanying low serum potassium values are in marked contrast to those observed when the serum potassium value is abnormally high. Thus, in patients with a low value, low-voltage QRS complexes and lowering or actual inversion of the T waves are observed. The ST segments may become depressed, and the QRS interval may be prolonged. In contrast, the electrocardiogram in patients with a high level may show an absence of the P waves, wide QRS complexes and high, peaked T waves.

SERUM POTASSIUM LEVELS IN DIABETIC COMA*

RICHARD H SINDEN, M D,† JAMES L TULLIS, M D,‡ AND HOWARD F ROOT, M D§

BOSTON

THE clinical importance of variations in the serum potassium level during treatment of diabetic coma has been emphasized by the reports of Holler,¹ Martin and Wertman,² Nicholson and Branning,³ Frenkel, Groen and Willebrands⁴ and Nadler, Bellet and Lanning.⁵ They reported low potassium values in certain patients undergoing treatment for diabetic coma, with fatal results unless suitable potassium solutions were administered promptly. On the other hand, studies of serum potassium levels in conditions of shock, cardiac or renal failure indicate that if potassium is given as a therapeutic measure to patients with impending or actual renal failure, a dangerously high level of potassium in the blood serum may also have a fatal result. Today, the physician responsible for the treatment of patients in diabetic coma, must

coma, such a loss may be very severe. This is especially true in previously undiagnosed cases.

It is the purpose of this paper to present 6 cases of diabetic coma in which routine potassium observations were made. All cases were studied in the George F Baker Clinic of the New England Deaconess Hospital, and are reported to show the effect of treatment without glucose on varying degrees of acidosis.

CASE REPORTS

CASE 1 This patient, a child, was not known to have diabetes until she was found in a drowsy state after several days of nausea and vomiting. On admission to the hospital the blood sugar was 400 mg per 100 cc, and the serum potassium was 3.1 milliequiv per liter. At the end of 17 hours of treatment the serum potassium fell to 2.5 milliequiv, but she had no referable symptoms and made an uncomplicated recovery with only 66 units of insulin and 1000 cc of physiologic saline solution intravenously (Table 1).

TABLE 1 Serum Potassium Levels in Diabetic Acidosis

CASE No	BLOOD SUGAR	PLASMA CARBON DIOXIDE	SERUM POTASSIUM		DURATION OF TREATMENT	INSULIN Dosage	TWENTY-FOUR-HOUR PARENTERAL INJECTION OF PHYSIOLOGIC SALINE SOLUTION	CLINICAL STATE
			ON ADMISSION	LOWEST				
	mg /100 cc	milliequiv /liter	milliequiv /liter	milliequiv /liter	hr	units	cc	
1	400	9	3.10	2.50	17	66	1 000	Patient drowsy
2	463	6	3.80	3.80	24	208	3 000	Patient semicomatose and anuric
3	450	5	3.75	3.12	20	270	2 500	Patient drowsy
4	805	9	4.43	3.60	20	450	3 000	Patient drowsy
5	296	10	4.30	4.10	10	165	2 000	Patient conscious
6*	765	10	5.40	3.30	4	340	4 000	Patient in coma with shock and anuria followed by death

*Included through the courtesy of Dr. Robert Brownlee

have constantly in mind the possibility that critical alterations in the level of blood serum potassium may result in a fatal outcome unless proper treatment is given in an early stage.

The causes of a decline in the serum level of potassium from a normal of around 5.0 milliequiv per liter to levels of 3.0 milliequiv or less are varied. It has long been known that during acidosis, particularly of the diabetic type, there is an immediate and increasing loss of potassium in the urine. This potassium comes chiefly from the cells, through disturbance in cellular permeability occurring during diabetic coma. A considerable loss of potassium in the urine may occur before extracellular levels are seriously affected. In cases of diabetic

CASE 2 A 19-year-old girl in diabetic acidosis for the second time had made very little attempt to control her diabetes. She had not followed the prescribed diet, nor had she checked her urine for sugar. Polyuria and polydipsia had been present for several weeks. Three days prior to admission abdominal pain had developed, followed in 48 hours by nausea and vomiting. After twenty-four hours of vomiting she was admitted to the hospital in a semiconscious state. The first hour's treatment consisted of intravenous administration of physiologic saline solution and 200 units of regular insulin. The admission potassium of 5.8 milliequiv per liter fell to 3.8 milliequiv in the next 24 hours. Recovery was uncomplicated.

CASE 3 This young woman followed very closely the pattern of Case 2, except that vomiting was present 48 hours prior to admission. The serum potassium levels were correspondingly lower, but her recovery was uneventful.

CASE 4 A middle-aged man had not been seen in the clinic for 2 years and had made very little effort to control his diabetes. In spite of the distressing symptoms of uncontrolled diabetes, he had continued eating a diet liberal in carbohydrate and maintained an inadequate insulin dosage. Nausea and vomiting began while he was on his way to the hospital from another state. After 4½ hours of vomiting he arrived at the hospital in fairly good condition with a blood sugar of 805 mg per 100 cc, and a carbon dioxide content

*From the George F Baker Clinic, New England Deaconess Hospital.

†Fellow in medicine, New England Deaconess Hospital.

‡Research fellow in biochemistry, Harvard Medical School.

§Associate in medicine, Harvard Medical School; physician in chief, New England Deaconess Hospital.

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DELAYED PNEUMONIA AND URTICARIA FOLLOWING BRONCHOGRAPHY

H E BASS, MD *

NEW YORK CITY

PNEUMONIA complicating bronchography has been described¹⁻⁴ Some of the cases previously reported have been attributed to infectious factors, owing to the carrying down of infecting organisms from the upper respiratory tract Waldbott¹ has emphasized the role of iodized oil in producing obstruction of the small bronchi followed by atelectasis of lung tissue and pneumonitis or massive collapse of a lung when a main bronchus is involved Other authors have reported cases of pneumonia believed to be due to an allergic reaction to the iodide component of lipiodol² All the reported cases, whether infectious or allergic, were characterized by a rapid onset of pneumonia, which usually occurred within twenty-four or forty-eight hours

A number of fatal cases have also been reported In 1 of these cases death occurred about seventy-five minutes after instillation of the iodized oil⁴ On post-mortem examination, both lungs were atelectatic, and the tracheobronchial tree was completely filled with thick, extremely tenacious mucus, which was found plugging even the smallest bronchioles These deaths were considered to be allergic and were directly attributed to the iodine fraction of the iodized oil used

More recently, 3 cases of pneumonia following the use of lipiodol in asthmatic patients were described that differed from those previously reported⁵ A delayed onset of pneumonia was noted, varying between nine and twelve days In addition,

these cases were characterized by certain allergic manifestations such as urticaria, blood eosinophilia and positive sensitivity tests with iodide-containing compounds The delayed pneumonic reaction was described as resembling the delayed reaction of serum sickness In view of the increasing use of lipiodol as a diagnostic procedure in the field of thoracic disease, one may expect to see more cases of this type of complication following bronchography

CASE REPORT

W P, a 59-year-old man, was admitted to the Municipal Sanatorium on July 17, 1947 There was no familial history of tuberculosis He stated that in November, 1940, he had suffered an attack of "pleurisy and pneumonia" for which he had been treated at home A chest x-ray film taken in 1941 was reported as normal He subsequently became an employee of the Municipal Sanatorium, where a chest x-ray examination in June, 1946, showed a healed primary complex, with calcifications at both hilar areas In July, 1947, a nonproductive cough developed, and a chest film revealed an area of infiltration in the left lung He was admitted to the Sanatorium as a suspected case of pulmonary tuberculosis

Physical examination was within normal limits except for a soft blowing systolic murmur transmitted to the left. The lungs were clear The blood pressure was 160/90 The sedimentation rate was 8 mm per hour (Westergren method) A Mazzini test was negative The urine showed no abnormal findings During the period of hospital observation, ten concentrated sputum smears and four gastric cultures were negative for tubercle bacilli X-ray examination of the chest revealed a mottled infiltration in the left-upper-lung field containing a central, oval-shaped area of homogeneous opacity This infiltration showed some increase in its extent shortly after admission, but subsequently regressed

Bronchoscopic examination performed on April 12, 1948, was negative, however, the left-upper-lobe bronchus could not be visualized It was believed that a bronchogram should be taken because of the possibility of an underlying bronchiectatic condition Accordingly, a bronchogram was taken

*Clinical instructor in medicine New York Medical College associate visiting physician Municipal Sanatorium Otisville New York.

A serum potassium value exceeding 12 milliequiv per liter may be and has been reported as fatal Paralysis may be flaccid or of the spastic type A more detailed discussion of electrocardiographic changes in various conditions is beyond the scope of this paper The subject is adequately covered by Milhorat⁸ and by Brown, Currens and Marchand⁹ and others^{5, 10, 11}

Currens and White¹² noted a fall in the serum potassium levels during treatment of patients with Addison's disease by means of desoxycorticosterone acetate They believed that the weakness associated with this treatment was often due to potassium loss The changes in the electrocardiogram accompanying high values of serum potassium are discussed by Tarail¹³ in a case of uremia and have also been described by Thorn,¹⁴ who cites the article on the clinical syndrome of potassium intoxication by Finch, Sawyer and Flynn¹⁵

Treatment of low serum potassium has proved successful in the cases of Holler,¹ Nicholson² and Frenkel,⁴ who use potassium chloride orally or begin with 100 cc of a 2 per cent solution intravenously Because glucose requires phosphorylation before it can be utilized, it seems wise to employ a combination of potassium and phosphate in cases that require intravenous administration of potassium salts In all such cases, however, the injection should be given slowly to avoid a transitory rise in the serum level to a dangerous concentration, and the diagnosis should be established with certainty either by means of actual serum analysis or unequivocal symptomatology and electrocardiographic findings For high serum potassium values, treatment of the underlying cause of renal insufficiency is indicated

The prevention of low serum potassium levels is possible by early and more rapid treatment of diabetic acidosis Every effort should be made to shorten the period of serious diabetic acidosis This means prompt use of insulin, when possible, long before the patient becomes drowsy Since, thus far, no patient has developed serious clinical hypokalemia unless intravenous glucose solution was administered during the first six to eight hours of treatment, one of the fundamental principles is to give no glucose in the first hours of treatment in diabetic acidosis

The excessive administration of glucose, especially with insulin, results in a rapid deposition of glycogen in the liver, associated with an intracellular shift of potassium, as shown by the experimental work of Fenn^{16, 17} Weissberg's¹⁸ patient received glucose intravenously and subsequently developed a serum potassium level of 1 milliequiv per liter—the lowest level recorded in the literature In the case reported by Tuynman and Wilhelm¹⁹ a low serum potassium level with respiratory difficulty developed after the patient had received glucose from the onset of treatment of diabetic coma They cite the work of Allott and

McArdle²⁰ in which 3 cases of periodic familial paralysis showed that attacks of paralysis, clinically identical with a naturally occurring attack, could be produced by the administration of glucose by mouth and by insulin but more consistently by glucose and insulin together

At the New England Deaconess Hospital during the three years ending April 1, 1948, 91 consecutive cases of diabetic coma have been treated without glucose and without a single death in spite of such complications as pneumonia, cerebrovascular accidents, heart disease, coronary occlusion and chronic nephritis The mere storage of excess glycogen has no value during the first few hours of the emergency in diabetic coma If 200 gm of glucose is given in the first few hours of treatment of diabetic acidosis, no more than 10 gm of glucose can be oxidized each hour²¹ The remainder must be excreted in the urine, deposited as glycogen (thereby producing a further reduction of serum potassium) or converted into fatty acids, as shown clearly by the isotopic studies of Stetten²²

Diabetic coma should always be considered an emergency in which the main object is to give an adequate amount of insulin in the first hours, to restore fluid balance promptly and to guard against potassium abnormalities In most cases, it is possible to start giving food orally after six to twelve hours It is the practice of this clinic to use food, such as oatmeal gruel and orange juice, which contain potassium, as soon as the stomach will retain it It is therefore timely and important in all cases of coma to wash out the dilated stomach and give an enema, to prepare the stomach for the taking of food at as early a period as possible Naturally, in patients remaining unconscious for twenty-four to forty-eight hours this procedure cannot be carried out, and intravenous feedings utilizing glucose become necessary In these cases the danger that hypokalemia will develop must be kept constantly in mind The prevention of fatal potassium intoxication may depend chiefly upon the avoidance of errors and the omission of potassium without definite indications

SUMMARY

Six cases of low potassium levels in diabetes from the George F Baker Clinic of the New England Deaconess Hospital are reported and discussed

Emergency serum potassium levels may occur during the treatment of diabetic coma and must constantly be kept in mind

The cause, diagnosis, treatment and prevention of high and low serum potassium levels are compared

For the prevention of dangerously low serum potassium values in diabetic coma, the omission of glucose administration during the first hours of treatment and more aggressive use of insulin are recommended

cases of lipiodol pneumonia originally reported⁵ sulfathiazole was employed but later discarded since no evident shortening of the period of illness was observed. It is possible that antihistaminic drugs exert a favorable influence on this type of pulmonary infiltration, and it is suggested that this form of therapy be employed.

A history of either familial or personal allergy is usually obtained in these cases. In such an event, iodine-sensitivity tests should be performed. The intracutaneous test with diodrast is perhaps as valuable as any.⁹ However, a negative skin test prior to bronchography is no safeguard against the development of a delayed lipiodol reaction.

In the case reported above, it should be noted that iodine-sensitivity tests were negative about two weeks after the disappearance of the urticarial eruption. Peck and his co-workers¹⁰ have described a similar finding in cases of urticarial reaction due to penicillin. They believe that although a positive reaction to a penicillin test is helpful in confirming a diagnosis of this type of allergy, a negative reaction does not exclude it. Since the reaction to penicillin may be positive in more than a third of such persons, the test is considered worth doing in an effort to prove that an eruption is due to penicillin. Furthermore, it has been pointed out by Lyons¹¹ that the induced urticarial form of penicillin allergy is often temporary, even transient. This observation has been borne out by Peck et al., who describe 2 patients whose initial reactions to the cutaneous test were positive, but in whom retests gave negative results. They imply that the mechanism by which the urticarial eruption is terminated is related to the reduction in sensitivity that may follow a violent reaction. It is possible that the status of the iodine-sensitivity test in cases of delayed lipiodol reactions is analogous to that obtaining in cases of delayed penicillin reactions.

In view of the foregoing observations, it is evident that an effort should be made to keep patients under observation for at least two weeks after bronchography. This is not always the case with clinic patients, who are frequently discharged after negative bronchographic tests. Iodine-sensitivity tests should be performed in patients who give a familial or personal history of allergy. In the presence of a positive test, bronchography might still be performed if the information to be gained therefrom is considered necessary for the carrying out of a surgical procedure such as pulmonary resection for localized bronchiectasis. In such cases an effort should be made to avoid overfilling of the bronchial tree. Trapping of lipiodol in the alveoli by explosive coughing should also be avoided. This can be accomplished by emptying of the bronchi, with postural drainage after completion of the examination. In addition, the use of antihistaminic drugs as a prophylactic measure against allergic reactions

for at least two weeks after bronchography is worthy of consideration.

SUMMARY

A case of delayed pneumonia and urticaria following bronchography in an allergic person is described. The mechanism of delayed reactions to iodized oil is discussed.



FIGURE 3 X-ray Film Taken on September 3, 1948
Note the decrease in the extent of the pneumonia in the left lung

The importance of keeping patients under observation for two weeks after bronchography is emphasized.

266 West End Avenue

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on the left side on July 31 (Fig. 1). About 8 cc. of lipiodol was instilled into both lobes of the left lung by means of an intratracheal catheter. No immediate untoward reaction was noted. The bronchogram showed suggestive bronchiectatic changes in the left-upper-lung field.

Fourteen days later the patient first noted the onset of productive cough. The temperature, which had been normal, rose to 100.4°F. At the same time, an extensive itching skin

that is characterized by a definite incubation period of one to three weeks may occur, the familiar phenomenon of serum sickness belongs in this category. Urticarial reaction of a serum-sickness type occurring after a definite incubation period is a well known complication of penicillin therapy. As described by Kolodny and Denhoff,⁷ this reaction is a delayed type because of the time needed for development of the newly induced sensitivity.

A similar time lag occurs in the type of pulmonary reaction to lipiodol in the case described above. The interval before symptoms appear may be from seven to fourteen days and even longer. The symptoms may be acute and may resemble the onset of a bacterial or virus pneumonia. Urticaria is frequently seen. Severe rashes of urticarial type occurring seven to ten days after injection of iodized oil have been described by Scadding.⁸ Cough, expectoration of a mucoid spu-

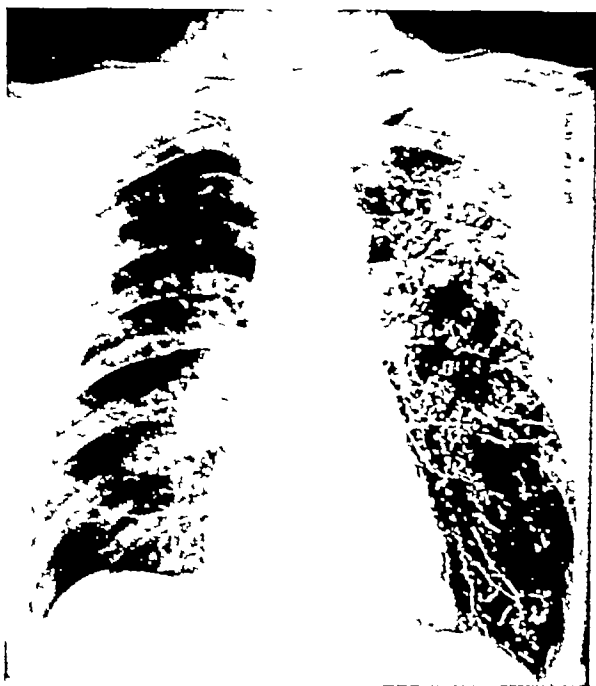


FIGURE 1 Bronchogram of the Left Lung, Taken on July 31, 1948

Note the suggestive bronchiectatic changes in the left-upper-lung field.

eruption which was urticarial and covered the arms, legs and trunk developed. On questioning, the patient stated that he had had a similar eruption, which he described as "hives," on several previous occasions.

A chest x-ray film taken on August 18 (Fig. 2) showed an extensive area of pneumonia occupying the lower-left-lung field. Numerous small densities representing retained lipiodol were visible throughout the left lung. Rales were heard at the left base for the first time. In spite of the rather extensive area of pneumonia visible on x-ray study, the patient appeared surprisingly comfortable. The temperature fell by lysis and reached normal levels after 5 days. A chest x-ray film taken on September 5 (Fig. 3) showed some regression of the area of pneumonic density, which still occupied the base of the lung. No allergic studies were performed at the time of the acute illness. However, a blood count done 2 weeks after the disappearance of the urticarial eruption did not reveal any increase in eosinophilic leukocytes. Iodine-sensitivity tests were also carried out at this time. An oral test with potassium iodide, a scratch test with lipiodol and an intracutaneous test with diodrast were negative.

DISCUSSION

Immediate allergic reactions to iodine in hypersensitive persons have been described.⁶ These reactions are analogous to those produced by serum therapy in patients sensitive to horse serum. In nonsensitized subjects a form of induced sensitivity



FIGURE 2 Film Taken on August 19, 1948, Showing Extensive Area of Confluent Pneumonia at the Left Base. There are numerous small area densities representing retained lipiodol in the remainder of the left lung.

tum and fever are prominent symptoms. The temperature is often low grade, whereas the extent of pulmonary involvement may be quite massive. Rales are heard over the involved portion of the lung field, usually at the base. Roentgenographic examination often reveals a confluent type of pneumonic density conforming to the area of distribution of lipiodol. Treatment is symptomatic. In the

cases of lipiodol pneumonia originally reported⁵ sulfathiazole was employed but later discarded since no evident shortening of the period of illness was observed. It is possible that antihistaminic drugs exert a favorable influence on this type of pulmonary infiltration, and it is suggested that this form of therapy be employed.

A history of either familial or personal allergy is usually obtained in these cases. In such an event, iodine-sensitivity tests should be performed. The intracutaneous test with diodrast is perhaps as valuable as any.⁹ However, a negative skin test prior to bronchography is no safeguard against the development of a delayed lipiodol reaction.

In the case reported above, it should be noted that iodine-sensitivity tests were negative about two weeks after the disappearance of the urticarial eruption. Peck and his co-workers¹⁰ have described a similar finding in cases of urticarial reaction due to penicillin. They believe that although a positive reaction to a penicillin test is helpful in confirming a diagnosis of this type of allergy, a negative reaction does not exclude it. Since the reaction to penicillin may be positive in more than a third of such persons, the test is considered worth doing in an effort to prove that an eruption is due to penicillin. Furthermore, it has been pointed out by Lyons¹¹ that the induced urticarial form of penicillin allergy is often temporary, even transient. This observation has been borne out by Peck et al., who describe 2 patients whose initial reactions to the cutaneous test were positive, but in whom retests gave negative results. They imply that the mechanism by which the urticarial eruption is terminated is related to the reduction in sensitivity that may follow a violent reaction. It is possible that the status of the iodine-sensitivity test in cases of delayed lipiodol reactions is analogous to that obtaining in cases of delayed penicillin reactions.

In view of the foregoing observations, it is evident that an effort should be made to keep patients under observation for at least two weeks after bronchography. This is not always the case with clinic patients, who are frequently discharged after negative bronchographic tests. Iodine-sensitivity tests should be performed in patients who give a familial or personal history of allergy. In the presence of a positive test, bronchography might still be performed if the information to be gained therefrom is considered necessary for the carrying out of a surgical procedure such as pulmonary resection for localized bronchiectasis. In such cases an effort should be made to avoid overfilling of the bronchial tree. Trapping of lipiodol in the alveoli by explosive coughing should also be avoided. This can be accomplished by emptying of the bronchi, with postural drainage after completion of the examination. In addition, the use of antihistaminic drugs as a prophylactic measure against allergic reactions

for at least two weeks after bronchography is worthy of consideration.

SUMMARY

A case of delayed pneumonia and urticaria following bronchography in an allergic person is described. The mechanism of delayed reactions to iodized oil is discussed.



FIGURE 3 X-ray Film Taken on September 3, 1948
Note the decrease in the extent of the pneumonia in the left lung

The importance of keeping patients under observation for two weeks after bronchography is emphasized.

266 West End Avenue

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MEDICAL PROGRESS

INDUSTRIAL MEDICINE

IRVING R. TABERSHAW, M.D.*

NEW YORK CITY

DURING the past year emphasis was placed on the social phases of industrial medicine. With the responsibility for control of the physical environment falling more and more to the technical specialists in industry, the factors involved in the worker's mental and social welfare were of growing concern to industrial physicians. Throughout the field greater co-ordination among all those involved, and more research and educational activities, were seen essential. As industrial medicine reaches full stature, the further necessity for it to assume a well defined place in the complex social scheme, consistent with the interests of the entire medical profession, becomes apparent. What is to be its scope — its limitations? The question is still unanswered.

The industrial physician today may be said to be at the crossroads¹. Without deviating from the basic tenets of the profession, he has been compelled to adapt himself to the demands of a fast-developing and changing industrial economy. Each

of the various forms of health insurance, group-term life insurance, accident and sick-benefit and pension plans has assumed a more significant part in relation to occupational medicine. The very nature of the industrial practitioner's work, dealing as it does with a specified segment of society, has placed him in an anomalous position. For example, although he adheres in theory to the established precept of the patient's free choice of a doctor, he cannot but violate it in actual practice.

Only further exploration of the situation — from the standpoints of industry, the medical profession and the community in general — can determine how far and how fast industrial medicine will travel. "The ultimate possibilities may be considered as narrowly or as broadly as vision and faith will permit."²

The continuing introduction of new manufacturing materials and processes brought scientific advances over a wide front, but no startling discoveries were announced. Many of the investigations into potential health hazards in various industries were incomplete. However, such important developments as were noted are reviewed below.

BERYLLIUM AND ATOMIC RADIATION

The epidemiology of beryllium poisoning is not completely understood, but the various clinical

manifestations produced by this metal have been more clearly defined and definite progress has been made toward its control.³⁻⁵ There is no longer any controversy about its toxicity since a significant health hazard can be shown to exist wherever beryllium dust or fume contaminates the atmosphere.

The contact dermatitis that appears in from three to ten days in workers processing beryl ore is of relatively minor consequence, but may be a precursor to the development of the acute or chronic form in susceptible persons. Approximately 50 per cent of workers will develop skin manifestations from contact with beryllium compounds that contain an acid radical, notably beryllium sulfate or beryllium fluoride.⁶ Ulceration may occur if a crystal of a soluble beryllium salt is introduced into the skin. These ulcerations do not heal readily until the base is curetted. Granulomatous skin lesions similar to sarcoid occur occasionally in people with the chronic form of pulmonary disease and are considered part of the generalized process. Grier et al.⁷ and Shook and Powell⁸ have recently described subcutaneous granulomas at the site of lacerations in people who have suffered cuts from fluorescent lamps coated with a zinc manganese beryllium silicate. The pathology of these granulomas is similar to that found in the lungs in cases of chronic pulmonary granulomatosis. Treatment by complete excision is effective. Disposal of burned-out fluorescent tubes is a hazard. Such tubes should be broken under water or disposed of intact, so as to prevent liberation of dust and possible implantation under the skin.

Exposure to soluble salts may produce chemical inflammatory changes in the respiratory tract and conjunctiva. Nasopharyngitis and tracheobronchitis are usually of transient nature and clear up upon removal from exposure. Acute pneumonitis is more serious and not infrequently fatal. The incidence and severity are related to the degree of exposure, the nature of the beryllium compound, particle size, surface area and so forth and to individual factors of susceptibility. The characteristic symptoms are dyspnea, cough, chest pain and cyanosis. Pulmonary infiltration undistinguishable by x-ray examination from generalized bronchopneumonia develops within a period of one to three weeks. Recovery, or death in the fulminating type, occurs within days to several months. At autopsy

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the lungs show a diffuse bronchopneumonitis similar to that in any chemical pneumonitis. The liver and spleen are enlarged and show changes consistent with an overwhelming chemical toxemia. The treatment is supportive and consists chiefly of oxygen, bed rest, antihistaminics and penicillin as a prophylactic.

These acute cases have occurred among workers engaged in the refining of beryl ore, in the manufacture of fluorescent lamps, in ceramics and in the machining of the pure metal. The use of beryllium copper products is not harmful, but when these alloys are ground, melted or tooled, contamination of the atmosphere with dust or fume may occur and produce some form of the disease. The highest incidence of acute pneumonitis is found in exposure to beryllium sulfate or fluoride, and cases have been known to develop after a single twenty-minute exposure to high concentrations.⁹ Maximum allowable concentrations have not been agreed upon but are judged to be in the range of 25 microgm per cubic meter for the acute disease. Engineering revisions of the industrial processes have reduced the incidence of acute pneumonitis to a very low level. Medical control by weekly examination, with particular emphasis on the vital capacity, which is diminished early, and prophylactic lav-off often lessen the severity and limit the tracheobronchial form from progressing.

The chronic form of the disease is characterized by a long delay between exposure and the onset of symptoms. Anywhere from four months to six years after the cessation of exposure, shortness of breath and loss of weight may develop. These symptoms continue until the patient dies, although some seem to have made a partial recovery. Pascucci,¹⁰ in a comprehensive review of the roentgen findings describes two types: a bilateral, uniformly widespread, diffuse granulomatous lesion and nodular infiltration. This fine, disseminated, granular type of infiltration is characteristic and not produced by any other definite pathologic entity. Pulmonary changes visible on x-ray study may exist without significant or any symptomatology. No clear-cut correlation can be drawn between the clinical features of the disease and the roentgenologic appearance of the lesions. Autopsy in the chronic cases shows a diffuse, nodular, granular, inflammatory response characterized by giant cells, epithelioid cells, plasma cells and inclusion bodies and by fibrosis. Pulmonary hypertension from reduction in the size of the pulmonary vascular bed is the most common cause of death. Other viscera, such as the hilar lymph nodes and the liver and spleen, show granulomatous infiltration and extensive fibrosis similar to that in the lung.

The vast majority of patients with a chronic disease give no history of an acute episode. Cases of the chronic disease have also occurred in people who were never exposed within an industrial plant

but lived in close proximity to a factory using a beryllium compound, as well as in the families of workers, the exposure apparently produced indirectly by contamination with work clothes. Follow-up examination on a number of workers with the acute disease indicates that most of them have recovered completely. But there are several cases that after a delay of months to years developed the typical clinical picture of the chronic disease. The presence, however, of such cases and the known long delay in onset leaves the question of progress from acute to chronic still undecided.¹¹

The prevention of the chronic case is difficult, but periodic examinations of exposed people, including x-ray films of the chest and vital-capacity determinations, are necessary for early diagnosis. Plant sanitation, as well as obligatory washing, showers and change of clothing, is essential for control. Substitution or segregation of beryllium processes will limit the incidence of the chronic disease.

Significant progress has been made in the determination of beryllium in air and body tissues.¹² Analyses of normal tissue indicate that the amount of beryllium is less than 0.05 microgm per 100 gm of wet-lung tissue and that normal urine contains no beryllium. Acute cases may show as much as 180 microgm per 100 gm of lung. The urine of exposed workers who show no symptoms may contain as much as 1.2 microgm of beryllium per liter, whereas those suffering from acute pneumonitis may show as much as 4.2 microgm of beryllium per liter of urine. The urine of patients with chronic granulomatosis varies from negative to 1.4 microgm of beryllium per liter. Lung tissue in chronic cases contains between 0.05 and 1.6 microgm. The variability and the technical difficulties of doing the beryllium determination in tissue indicate that reliance should not be placed on beryllium tissue content as pathognomonic of the disease, but rather as evidence of exposure to beryllium.

Industrial development of atomic energy has not progressed to the point where it is of significance to most industrial physicians. Results of experiments, however, by workers associated with the atomic program have appeared in quantity in the literature. Of particular interest to the industrial physician is the evidence that hematologic studies for the reduction of lymphocytes in the peripheral blood are still the most sensitive indicator of exposure to ionizing radiation.¹³ More caution in exposure to radiation is beginning to be prevalent among health physicists, who suggest that the tolerance dose be decreased from 0.1 r to 0.05 r per day, or a maximum of 0.3 r per week.¹

PNEUMOCOINOSIS

Although a large number of articles were published describing the occurrence, distribution and characteristics of silicosis in various dusty indus-

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should be reduced from 75 to 35 parts per million, and Forssmann and Frickholm⁴⁰ state that exposure to benzene creates an increased demand for vitamin C and that an extra supply increases the resistance to the effects of this toxin. Clinton⁴¹ describes an accident in which a large amount of selenium was released in the air. No systemic toxic effects were noted, and only severe local irritation occurred. A comprehensive review of the acute effects and treatment of chlorine inhalation was described by Chasis et al.⁴² when over 400 people were accidentally poisoned with this gas after rupture of a chlorine tank. No chronic pulmonary sequelae were noted in any of the patients who were followed for sixteen months although some had persistent anxiety reactions.

DERMATITIS

With occupational dermatitis constituting approximately 65 per cent of all cases of occupational diseases,⁴³⁻⁴⁴ the dermatologic problem continued to demand constant vigilance and study on the part of the industrial physician. No outstanding developments were reported in this field, but over-all methods of control were reviewed by a number of authorities. All were agreed on the importance of preventive measures such as provision of proper cleansing facilities, substitution of nonirritating materials when possible, use of protective clothing and creams, and careful placement of employees.

Criteria for determining the industrial status of skin diseases were discussed by Bulmer,⁴⁵ Macauley,⁴⁴ Downing⁴⁶ and others. About 40 per cent of a large number of cases of employees claiming compensation for occupational dermatitis, on which Downing reported, were proved to be of nonindustrial origin. Approximately 20 per cent or less of industrial skin diseases are allergic, according to Tolmach,⁴⁶ but the percentage was difficult to determine since diagnoses were frequently based on inaccurate histories or solely on patch tests, improperly applied.

The skin hazards in 114 occupations and the newer therapeutic agents, as well as dermatoses due to wearing apparel and to various cosmetic preparations, were considered by Schwartz et al.⁴⁷ In the last-named category, a cause of dermatitis, mentioned elsewhere,⁴⁸ is prolonged or frequent contact with the so-called "cold" permanent hair-waving preparations. Employees' exposures to skin hazards away from work, as well as on the job, should be taken into account before the physician renders his final opinion about the etiologic agent in each case.⁴⁹ Investigations were reported on different occupations, such as flour allergy with cutaneous reactions,⁵⁰ paint-factory workers and painters with occupational dermatoses,⁵¹ workers exposed to pitch, tar or tar products⁵²⁻⁵³ and farmers and others suffering from grain itch.⁵⁴⁻⁵⁵ Other occupations studied for their skin hazards were those of long-

shoremen⁵⁶ and workers in the jewelry industry⁵⁷ and in the poultry industry.⁵⁸

Numerous procedures for the control of specified occupational skin hazards were recommended. For employees working with chromium salts, the use of a nasal paste of 5 per cent bismuth subnitrate in soft paraffin was found effective to prevent perforation. This method was adopted in German chromium plants, where 30 to 40 cases of lung cancer had occurred.⁵⁹ Reviewing the poisonous properties of DDT, Van Huut⁶⁰ advised the wearing of synthetic-rubber gloves and provision of good ventilation where it is being used. Solvents as vehicles for DDT were studied and reported on from the standpoint of their photosensitizing action on the skin.⁶¹ Carbitol, which is being used more and more in cosmetic or other preparations for the skin, can constitute a health hazard, if uncontrolled.⁶² Temporary loss of hair among workers in neoprene-manufacturing plants occurs only in the polymerization areas, it was found.⁶³ No satisfactory treatment or protective headgear was developed, but the condition was controlled or eliminated by frequent and complete changes of air in the polymerization areas. In general, precautions should be taken not only in the particular location where any irritant fume or solvent mist is present but also in nearby areas to which air currents can transport such agents, according to Campbell,⁶⁴ who observed several cases of dermatitis due to this indirect type of exposure.

The testing of a large number of protective-glove materials for their permeability to tetraethyl lead and ethylene bromide led Calingaert and Shapiro⁶⁵ to conclude that nylon and also nylon compounded with neoprene are the most impermeable and best suited for this purpose. Various barrier creams were investigated by Cumming⁶⁶ and others, with a view to lowering the high incidence of dermatitis in industries manufacturing explosives, particularly tetryl and other nitrocompounds. A new protective cream, with liquid paraffin forming the basis, was developed. Other barrier creams, for workers handling the soluble phenols and cresol formaldehyde products, and for workers exposed to pitch, were reported by Weldon.⁶⁷

REHABILITATION AND JOB PLACEMENT

The proposition that rehabilitation of the disabled worker is a vital function of industrial medicine is being accepted more and more widely, here and abroad. The need for veterans' rehabilitation programs had been recognized and acted upon early in the post-war period, but until more recently such programs were only very rarely extended to include the physically impaired among civilian industrial workers. That a large potential of human productivity was being by-passed by industry — to the detriment of industry itself, as well as of the community at large — was frequently noted. To overcome the resistance of industry in accepting phys-

tries, no significant revisions were suggested in the diagnosis, epidemiology, management or control of the disease. It is interesting in this connection to note the finding of McCormick et al.¹⁵ that in the processing of leaf tobacco the inhalation of hygienically significant free silica in the tobacco dust may present a hazard.

Exposure factors were more carefully studied in several articles, with special reference to particle-size distribution. Hatch and Kindsvatter¹⁶ indicate that particles below 0.5 microns may be of greater import than was previously thought. The importance of quantitative evaluation of the influence of particle size upon toxic activity of dust is stressed,¹⁷ and Holden and his associates¹⁸ state that the free silica content of the fraction below 5 microns provides a more significant measure of the silicosis dust potentiality than the total dust analysis.

More cases of bagassosis, a pulmonary disease resulting from the inhalation of bagasse dust, were reported.¹⁹ Bagasse, a sugar-cane waste product, is used in the manufacture of insulating and acoustic board, and its dust produces sudden cough, severe dyspnea, chills and fever and occasional hemoptysis. X-ray study discloses diffuse mottling of both lungs, which clears in from two weeks to several months. Numerous etiologies have been suggested,²⁰ but the most recent work of Schneider et al.²¹ indicates that the cause of the disease is *Aerobacter cloacae* (a soil bacterium also present in cotton) acting in conjunction with the inhaled particles of the irritant bagasse dust.

Aluminum and some of its oxides have been shown experimentally to inhibit the action of silica in producing silicosis, and extensive prophylactic and therapeutic clinical trials are presently under way. A new apparatus for dispensing the aluminum hydroxide dust is described by Church and Ingram.²² Riddell²³ cautions, however, against the acceptance that the treatment is of value since no conclusive objective evidence has as yet been brought out. The effect of aluminum inhalation in human beings is apparently chiefly psychologic in its effect. Although most of the evidence indicates that alumina is harmless, the finding of pulmonary fibrosis and pneumothorax in workers exposed to bauxite in the manufacture of corundum has been reported.²⁴ The fume generated in this process consists of finely divided silica and amorphous alumina. Similar experiences from Germany and Sweden²⁵ corroborate that some processes involving the manufacture of aluminum compounds produce a form of pneumoconiosis. A field study on the effect of alumina and silica is provided in the pottery industry, in which workers are exposed to finely powdered alumina and flint.²⁶ This group of workmen, although daily exposed to finely powdered alumina in greater intensity and over a longer period than existing methods of treatment could cope with, showed not only new cases of silicosis but also known

cases of the advanced form. Baetjer,²⁷ in a study of the effect of Portland-cement dust reported no effect on animal resistance to lobar pneumonia, differing in this respect from the effects of quartz and feldspar dust.

SPECIFIC CHEMICALS

The toxicologic properties of a host of new industrial chemicals were reported during the past year. Revisions of certain phases of knowledge of some of the older ones were also made. The absorption of lead through the skin was found to be very small for nonvolatile compounds such as lead oleate, lead acetate and lead arsenate. Volatile compounds, notably lead tetraethyl, penetrate the skin with great ease.²⁸ The maximum allowable concentration for lead, which has been standardized for some years at 1.5 mg per 10 cubic meters of air, has been criticized as not always applicable.²⁹ Insoluble lead compounds such as lead chromate are definitely less toxic, and review and standardization of each type of lead compound has been suggested. Experimental studies on the use of BAL, which had been found efficacious³⁰ in arsenic and mercury poisoning, showed that although it increases lead excretion, it apparently has no effect on decreasing the toxicity of the absorbable lead. Other lead antidotes, specifically a soluble dithizone, are being studied. A spectrophotometric method for rapid lead urinalysis shows great promise as a screening technic for lead absorption.³¹

Considerable attention was paid to the carcinogenic properties of various industrial chemicals. Evidence is accumulating rapidly that exposure to chromates greatly increases the incidence of pulmonary and other carcinomas.³² The number of cases of cancer in a factory handling arsenic indicates that there is an excess of deaths from this cause in such workers.³³ Carcinomas of the bladder from aniline do not occur because exposure is sufficiently well controlled, but beta-naphthylamine and benzidine still produce cases.^{34, 35}

Princi³⁶ doubts that cadmium, which is considered a severe industrial toxin, is capable of producing chronic effects. Friberg,³⁷ however, describes kidney damage in a group of workers exposed to nickel and cadmium, although previous reports in the literature give no direct evidence that either of these metals causes pathological changes in the kidney. An important contribution to the toxicity of sodium fluoride has been made by the Public Health Service³⁸ in a study of exposure at open-hearth furnaces. Irritating upper respiratory symptoms may occur, but there is no evidence of any pulmonary cardiovascular or skeletal findings of fluorosis. Also, no effect was noted on the teeth or tissues of the oral cavity in workers using sodium fluoride.

Hardy and Elkins³⁹ reached the conclusion that the maximum allowable concentration for benzene

should be reduced from 75 to 35 parts per million, and Forssmann and Frvholm⁴⁰ state that exposure to benzene creates an increased demand for vitamin C and that an extra supply increases the resistance to the effects of this toxin. Clinton⁴¹ describes an accident in which a large amount of selenium was released in the air. No systemic toxic effects were noted, and only severe local irritation occurred. A comprehensive review of the acute effects and treatment of chlorine inhalation was described by Chasis et al.⁴² when over 400 people were accidentally poisoned with this gas after rupture of a chlorine tank. No chronic pulmonary sequelae were noted in any of the patients who were followed for sixteen months although some had persistent anxiety reactions.

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tries, no significant revisions were suggested in the diagnosis, epidemiology, management or control of the disease. It is interesting in this connection to note the finding of McCormick et al.¹⁵ that in the processing of leaf tobacco the inhalation of hygienically significant free silica in the tobacco dust may present a hazard.

Exposure factors were more carefully studied in several articles, with special reference to particle-size distribution. Hatch and Kindsvatter¹⁶ indicate that particles below 0.5 microns may be of greater import than was previously thought. The importance of quantitative evaluation of the influence of particle size upon toxic activity of dust is stressed,¹⁷ and Holden and his associates¹⁸ state that the free silica content of the fraction below 5 microns provides a more significant measure of the silicosis dust potentiality than the total dust analysis.

More cases of bagassosis, a pulmonary disease resulting from the inhalation of bagasse dust, were reported.¹⁹ Bagasse, a sugar-cane waste product, is used in the manufacture of insulating and acoustic board, and its dust produces sudden cough, severe dyspnea, chills and fever and occasional hemoptysis. X-ray study discloses diffuse mottling of both lungs, which clears in from two weeks to several months. Numerous etiologies have been suggested,²⁰ but the most recent work of Schnitzer et al.²¹ indicates that the cause of the disease is *Aerobacter cloacae* (a soil bacterium also present in cotton) acting in conjunction with the inhaled particles of the irritant bagasse dust.

Aluminum and some of its oxides have been shown experimentally to inhibit the action of silica in producing silicosis, and extensive prophylactic and therapeutic clinical trials are presently under way. A new apparatus for dispensing the aluminum hydroxide dust is described by Church and Ingram.²² Riddell²³ cautions, however, against the acceptance that the treatment is of value since no conclusive objective evidence has as yet been brought out. The effect of aluminum inhalation in human beings is apparently chiefly psychologic in its effect. Although most of the evidence indicates that alumina is harmless, the finding of pulmonary fibrosis and pneumothorax in workers exposed to bauxite in the manufacture of corundum has been reported.²⁴ The fume generated in this process consists of finely divided silica and amorphous alumina. Similar experiences from Germany and Sweden²⁵ corroborate that some processes involving the manufacture of aluminum compounds produce a form of pneumoconiosis. A field study on the effect of alumina and silica is provided in the pottery industry, in which workers are exposed to finely powdered alumina and flint.²⁶ This group of workmen, although daily exposed to finely powdered alumina in greater intensity and over a longer period than existing methods of treatment could cope with, showed not only new cases of silicosis but also known

cases of the advanced form. Baetjer,²⁷ in a study of the effect of Portland-cement dust reported no effect on animal resistance to lobar pneumonia, differing in this respect from the effects of quartz and feldspar dust.

SPECIFIC CHEMICALS

The toxicologic properties of a host of new industrial chemicals were reported during the past year. Revisions of certain phases of knowledge of some of the older ones were also made. The absorption of lead through the skin was found to be very small for nonvolatile compounds such as lead oleate, lead acetate and lead arsenate. Volatile compounds, notably lead tetraethyl, penetrate the skin with great ease.²⁸ The maximum allowable concentration for lead, which has been standardized for some years at 1.5 mg. per 10 cubic meters of air, has been criticized as not always applicable.²⁹ Insoluble lead compounds such as lead chromate are definitely less toxic, and review and standardization of each type of lead compound has been suggested. Experimental studies on the use of BAL, which had been found efficacious³⁰ in arsenic and mercury poisoning, showed that although it increases lead excretion, it apparently has no effect on decreasing the toxicity of the absorbable lead. Other lead antidotes, specifically a soluble dithizone, are being studied. A spectrophotometric method for rapid lead urinalysis shows great promise as a screening technic for lead absorption.³¹

Considerable attention was paid to the carcinogenic properties of various industrial chemicals. Evidence is accumulating rapidly that exposure to chromates greatly increases the incidence of pulmonary and other carcinomas.³² The number of cases of cancer in a factory handling arsenic indicates that there is an excess of deaths from this cause in such workers.³³ Carcinomas of the bladder from aniline do not occur because exposure is sufficiently well controlled, but beta-naphthylamine and benzidine still produce cases.^{34, 35}

Princi³⁶ doubts that cadmium, which is considered a severe industrial toxin, is capable of producing chronic effects. Friberg,³⁷ however, describes kidney damage in a group of workers exposed to nickel and cadmium, although previous reports in the literature give no direct evidence that either of these metals causes pathological changes in the kidney. An important contribution to the toxicity of sodium fluoride has been made by the Public Health Service³⁸ in a study of exposure at open-hearth furnaces. Irritating upper respiratory symptoms may occur, but there is no evidence of any pulmonary cardiovascular or skeletal findings of fluorosis. Also, no effect was noted on the teeth or tissues of the oral cavity in workers using sodium fluoride.

Hardy and Elkins³⁹ reached the conclusion that the maximum allowable concentration for benzene

should be reduced from 75 to 35 parts per million, and Forssmann and Frickholm⁴⁰ state that exposure to benzene creates an increased demand for vitamin C and that an extra supply increases the resistance to the effects of this toxin. Clinton⁴¹ describes an accident in which a large amount of selenium was released in the air. No systemic toxic effects were noted, and only severe local irritation occurred. A comprehensive review of the acute effects and treatment of chlorine inhalation was described by Chasis et al.⁴² when over 400 people were accidentally poisoned with this gas after rupture of a chlorine tank. No chronic pulmonary sequelae were noted in any of the patients who were followed for sixteen months although some had persistent anxiety reactions.

DERMATITIS

With occupational dermatitis constituting approximately 65 per cent of all cases of occupational diseases,⁴³⁻⁴⁴ the dermatologic problem continued to demand constant vigilance and study on the part of the industrial physician. No outstanding developments were reported in this field, but over-all methods of control were reviewed by a number of authorities. All were agreed on the importance of preventive measures such as provision of proper cleansing facilities, substitution of nonirritating materials when possible, use of protective clothing and creams, and careful placement of employees.

Criteria for determining the industrial status of skin diseases were discussed by Bulmer,⁴⁵ Macauley,⁴⁴ Downing⁴⁶ and others. About 40 per cent of a large number of cases of employees claiming compensation for occupational dermatitis, on which Downing reported, were proved to be of nonindustrial origin. Approximately 20 per cent or less of industrial skin diseases are allergic, according to Tolmach,⁴⁶ but the percentage was difficult to determine since diagnoses were frequently based on inaccurate histories or solely on patch tests, improperly applied.

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ically impaired workers because of increased liabilities under the workmen's compensation laws, New York State amended its Second Injury Fund to provide equitable adjustment of the liability an employer assumes in the employment of a worker with any permanent physical impairment.⁶⁷

Hanman⁶⁸ observed that the physically handicapped comprise a majority of the population. He pointed further to the numerous studies that have shown that disabled employees, properly placed in industry, can be equal or superior to others. This estimation was proved correct in various reports on actual experience in the selective placement of the so-called unfit. The New Jersey Rehabilitation Commission⁶⁹ and the Federal Bureau of Labor Statistics reported that experience has shown the physically handicapped to be more efficient, to lose less time away from the job, to have more social contacts and to be less prone to accidents (except for the hard of hearing) than other employees.

Opinion about the ideal type of organization and sponsorship of rehabilitation programs varied. Rehabilitation centers supplementing hospitals and set up on a community basis were foreseen for the future by Deaver,⁷⁰ and the present lack of such centers was deplored by Rusk⁷¹ and various others. A co-ordinated rehabilitation bureau to serve the entire district of Lyons, France, was proposed as a model by Gauthier et al.⁷² That society has an undeniable responsibility toward the economic and social restoration of the handicapped was not disputed, but industry's share in this responsibility was questioned. Management's hesitancy to hire workers not in perfect health was considered valid by Luongo,⁷³ who pointed to the risks of subsequent unmerited compensation appeals, especially in cases of tuberculosis, silicosis and mental disorders. On the other hand, Pringle⁷⁴ expressed a broader concept of industrial health as indivisible into "health-at-home" and "health-at-work" categories.

The practical benefits in industry's employment of the handicapped were publicized by a number of organizations, such as the National Association for the Employment of the Handicapped and the Office of Vocational Rehabilitation of the Federal Security Agency.⁷⁵ It was estimated that approximately 8,000,000 men, including veterans and civilians, would require the services of rehabilitation and vocational-guidance centers.⁷¹ Yet, rather than increasing, the number of those applying to existing rehabilitation centers for training and jobs decreased.

A prerequisite in any industrial rehabilitation program is the co-operation of labor, industry, medicine and sociology,⁷⁶ but rehabilitation is primarily a function of surgical and medical care.⁷⁷ Close co-ordination between job assessor and physician is necessary, according to Lloyd,⁷⁸ who gave a detailed description of the job analysis method used in matching the rehabilitated worker to the job, as well as a rapid and practical system of re-

cording the analytical data. For workers injured in industry, Aitken⁷⁹ found that aftercare, with a view to the patient's re-employment, has been generally inadequate.

Attention was focused on the rehabilitation needs and potential productivity of persons disabled by specified illnesses or injuries: tuberculosis, cardiac conditions, rheumatic ailments and loss of limbs. Sander,⁸⁰ in a report on tuberculosis in industry, showed that it was unnecessary to refuse employment to job applicants with a history of this disease. He presented a guide for establishing the worker's clinical status and effecting proper placement and follow-up examinations. The difficulties encountered by persons with arrested tuberculosis were described by Moller.⁸¹ In workers with heart disease, the cardiac clinic and employment service should co-operate to appraise each patient's physical capacities, analyze the physical demands of the job and match the latter against the former.⁸² Sprague⁸³ advised complete cardiac studies of cardiac patients before employment is considered and regular reclassification checkups with the use of electrocardiography for those already employed. The training and placing in suitable work of rheumatic patients was discussed by Bonni,⁸⁴ and in another report the problem of dealing with injuries in workers affected by arthritic conditions was explored.

In the rehabilitation of civilians with amputations Kessler⁸⁵ stressed the lack of, and great need for, a program like that developed by the armed forces. The lack of such a service for persons disabled in industrial accidents was noted by Devesa⁸⁶ in Spain, where the patient is offered the alternative of a cash settlement or a prosthesis of poor quality and usually chooses the former.

PSYCHIATRY

Investigation in the field of industrial psychiatry suggested vast possibilities for the future. The urgent need for wider application of the psychiatric methods already proved and for further study and greatly expanded training programs was repeatedly stressed. Several surveys showed a direct relation between the mental and emotional health of workers and their proneness to frequent accidents, general unrest on the job — as evidenced in lateness and absenteeism — and even physical illness. Hence, attention to the psychologic impairment of employees was advocated as a cost-saving necessity for industry, if not as an obligation to the community.

Without proposing specific methods of administering psychiatric services, numerous spokesmen for industrial management and the medical profession urged consideration of human relations and of the emotional element involved in industrial employment.⁸⁷⁻⁸⁸ Striking proof of the importance of psychologic factors in industrial efficiency was shown in a detailed study of the incidence of neuro-

sis in factory workers, the factors predisposing to it and its effects on production, reported in England⁵⁹ Of 3000 workers, 10 per cent had suffered definite neurosis and 20 per cent had suffered minor neurosis Neurotic illness caused from a quarter to a third of all absence due to illness The same frequency was found in workers at higher and lower levels of skill and earnings The incidence was greater among women than men The survey showed that neurosis was most common among workers with few social contacts and unsatisfactory domestic circumstances, and especially among those who disliked or were bored by their jobs Fatigue, inadequate diet and lack of proper lighting on the job contributed to neurotic illness

That mental incapacity in industry is related to group morale was established by Brodman and Hellman,⁵⁹ who found that frequent short illnesses occurred in departments where frequent lateness — a concomitant of poor morale — was also noted The data further brought out that the individual's work morale is definitely influenced by the group and that different work groups have dissimilar morale

Eliminating basic causes of employee maladjustment would do away with many grievances that start as minor complaints⁹⁰ The role of the individual employee's supervisor or foreman in this type of adjustment was discussed by Brodman,⁹¹ Marrow,⁹² Maier⁹³ and others Training programs were suggested to bring to first-line supervisors an awareness of, and ability to meet, the underlying complicated problems of emotionally disturbed workers

Mounting concern for the costly effects of alcoholism among industrial employees was revealed in the growing number of studies on the subject Bacon⁹⁴ estimated that of approximately 4,000,000 alcoholic persons in the United States, about 2,890,000 are men between the ages of thirty and sixty, and about 1,370,000 "chronic, excessive and compulsive drinkers are fairly regularly employed in industry" The problem is more susceptible to correction in industry than in the community at large and can be met with the help of psychiatry

The industrial physician must bring himself up to date psychiatrically, according to Moorad,⁹⁵ who quoted statistics to show that from 85 to 90 per cent of accidents are due to "human factors" Healthy workers with personality disorders should be the responsibility of industry, for its own benefit They not only have repeated accidents, Moorad declared, but also contribute heavily to absenteeism and project their dissatisfaction and low morale among their fellow employees He described five prominent types, showing how and why each can cause accidents The first step, in any case, is proper placement or elimination, but workers with neurotic tendencies should not be eliminated entirely, since cure and adjustment are possible through psychiatric treatment⁹⁶ Patients with neurosis and employ-

ment difficulties have been rehabilitated with notable success at a unique industrial neurosis unit at Sutton Hospital in England⁹⁷

Reports on various procedures used in placing and counseling employees indicated an increasing interest in this aspect of industrial psychiatry The Rorschach (ink-blot) test is a valuable supplement to the customary testing and interviewing technics Noting that 1 out of every 11 employees have serious temperamental difficulties, Armbruster⁹⁸ held that job applicants should be tested not only for aptitude but also for interest in the work, motivation, general intelligence and temperament The use of employee tests should be accompanied by an understanding of "the dynamic aspects of personality problems and of the complicated processes involved in group adjustment"⁹⁹

Counseling technics were discussed by Himler,¹⁰⁰ who observed that "skilled listening constitutes the major part of the counselor's therapeutic armamentarium" In another report, industrial non-directive counseling was found to have advantages over clinical nondirective counseling, because of the more casual and intimate contact in the plant as compared to that found in clinical psychotherapy¹⁰¹

Chronic industrial fatigue was seen as a contributing factor to emotional instability, absenteeism and proneness to accidents The installation of "color conditioning," making scientific use of wall and fixture paints, was reported in several cases to result in less eyestrain and fatigue and greater efficiency,¹⁰² whereas noise control was given as another means of reducing mental fatigue and abnormal emotional reactions¹⁰³ In discussing industrial fatigue, Carozzi¹⁰⁴ argued that more important than adapting machine and working conditions to the worker was attention to him as a human being, in his personal, family and broader social settings

A notable step forward was seen in the inauguration of a pioneer program to train psychiatrists for the industrial-relations and labor field at Cornell University¹⁰⁵ At the same time, at Harvard University and Massachusetts Institute of Technology scientific investigation was under way into the social — as distinguished from the physical — working environment of industrial employees

EDUCATION

Educational facilities for physicians intending to enter the industrial service were extended here and there, by a few universities, and with the co-operation of certain local or state medical societies, hospitals and industries, but a general, standardized program was still lacking However, progress was made in orienting individuals and organizations, both professional and industrial, toward accepting the inevitability of specialized industrial medical education With emphasis shifting toward the preventive and research aspects of the field, there was

little question that more trained and experienced occupational practitioners were needed

Medical educators, in large measure, have failed to adapt their training or practice to meet the needs of the present-day American community, Kehoe¹⁰⁶ pointed out. No comparable field of medicine has offered so few opportunities for formal training as that of industrial hygiene.¹⁰⁷ Lacking specialized educational facilities, industrial medical directors "have evolved via the school of experience from general practitioners, general surgeons and internists," Brown¹⁰⁸ declared. Because well trained industrial medical men "are not to be found," he added, "there are an enormous number of small plants of every description without any medical department much less a health program."

There must be accord among industrial physicians, themselves, on the scope, objectives and methods of their practice, before teaching centers can be expected to provide the necessary instructional facilities, Buchan¹⁰⁹ asserted. Industry too "must make known in no uncertain terms its needs in medical and ancillary personnel, its needs in applied and fundamental industrial medical research."

According to several proposed plans, graduate work should include, as an essential, in-plant service or residency. One large industry's in-plant fellowship program, conducted with the co-operation of a leading medical school and said to be the first of its kind in this country, was described.¹¹⁰ In most of the graduate courses now offered, "a major defect is the lack of opportunity to give an adequate on the job experience."¹⁰⁷

In the undergraduate curriculum, Kronenberg¹¹¹ finds that "industrial medicine must be introduced and expanded if medical education is to be progressive and useful and meet present-day needs." Certain groundwork material can be introduced by "infiltrative tactics" in preclinical departments, Goldwater¹¹² stated, but industrial medicine, if regarded as a specialty, "obviously calls for special graduate or postgraduate training." He suggested that schools of public health were appropriate centers for training industrial physicians, as well as industrial nurses, engineers and chemists, and cited the inauguration of such a program at Columbia University. Among the nation's nine schools of public health, courses in industrial health and opportunities for advanced specialization in the field are generally provided.¹¹³

A crucial factor in the solution of the educational problem is the lack of established standards. Some progress was shown in the fact that residencies in the specialty of occupational medicine have been placed on a formal basis comparable to other residencies in line with the plan adopted by all certification boards.¹¹⁴ The chief difficulty remaining is to obtain suitable applicants and establish the fellowships themselves. From the viewpoint of the prospective candidates in the field of industrial medicine

both inducement and financial means were seen to be lacking.¹¹⁵ The failure of the medical profession to dignify industrial medicine with official recognition as a specialty was considered a deterrent to students in deciding to enter the field. Scholarship and fellowship funds are being established, and industry itself has been urged to subsidize graduate training.¹¹⁶

MEDICAL SERVICES

Marked inequalities persisted in the medical services provided for industrial workers in different localities and from one industry to another. In general, in-plant medical services were maintained and continually improved upon by large industries, but were still inaccessible to small industries. To what extent this disparity affects the whole picture can be judged by the fact that small concerns are estimated to constitute 99 per cent of the nation's industrial plants,¹¹⁷ employing about 60 per cent of the total labor force.¹¹⁸

No country-wide studies of the situation were reported on, but several surveys of limited groups of representative plants were made. One such study of 565 plants employing 500 or fewer workers showed that only a few provided even a minimum of medical care.¹¹⁷

In Illinois it was found that more than 12,000 small industrial establishments had no medical service,¹¹⁹ whereas in Connecticut,¹²⁰ 1400 plants employed a total of 119 physicians.

Diverse approaches to the small plants' health problem were recommended. In France¹²¹ small businesses affiliate to form a joint medical unit, a system successfully tried in one Pennsylvania community.¹²² Management-labor "safety committees"¹²³ have been organized in industries of all sizes in Sweden and also have functioned satisfactorily in some small or medium plants here.¹²⁴ In one plant of less than 1000 employees a single, full-time male nurse effectively directed the combined health, safety and welfare departments.¹²⁵ Regional programs were instituted, mostly advisory in character, in various centers such as Chicago,¹²⁶ and Washington, D. C.,¹²⁷ and in areas of Wisconsin,¹²⁸ Indiana¹²⁹ and Nebraska.¹³⁰

A total of 58 industrial-hygiene units were functioning under the Industrial Hygiene Division of the United States Public Health Service, with 43 per cent of the budget deriving from state and local funds and the remainder from federal funds.¹³¹

Among new types of service reported from abroad was that in Manitoba, Canada.¹³² An industrial-hygiene bureau, operating in a comparatively thinly populated region, attempted to improve the health conditions in small plants and conducted a program featuring portable x-ray equipment, plant surveys and stipple-cell counting service. For railway workers in France, four trains fitted with x-ray apparatus were traveling all over the country and

stopping wherever the equipment was needed for employees' periodic physical examinations¹³³

The extension of medical-service programs to all industries was urged not only on humanitarian grounds but also on the basis of increased production. On-the-job medical care was estimated to reduce absenteeism due to sickness up to 60 per cent¹¹⁷

The expansion of existing services in larger plants included the building of new dispensaries and the addition of various specialists to the medical-department staffs. Periodic physical examinations and special checkups for workers in hazardous areas were increasingly the custom¹²⁴

Heightened interest in industrial eye and dental programs was expressed^{135 136}. Teamwork of all those responsible for the employees' welfare was declared essential in the provision of health services. Derryberry¹³⁷ called on industrial physicians to realize "that the medical sciences are but a part of the total technology which must be brought to bear on the maintenance of health and the prevention of disease and disability."

The value of proper record keeping in industrial medical departments was frequently stressed and various suggestions for improved recording systems were offered¹³⁸⁻¹⁴¹

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little question that more trained and experienced occupational practitioners were needed

Medical educators, in large measure, have failed to adapt their training or practice to meet the needs of the present-day American community, Kehoe¹⁰⁶ pointed out. No comparable field of medicine has offered so few opportunities for formal training as that of industrial hygiene.¹⁰⁷ Lacking specialized educational facilities, industrial medical directors "have evolved via the school of experience from general practitioners, general surgeons and internists," Brown¹⁰⁸ declared. Because well trained industrial medical men "are not to be found," he added, "there are an enormous number of small plants of every description without any medical department much less a health program."

There must be accord among industrial physicians, themselves, on the scope, objectives and methods of their practice, before teaching centers can be expected to provide the necessary instructional facilities, Buchan¹⁰⁹ asserted. Industry too "must make known in no uncertain terms its needs in medical and ancillary personnel, its needs in applied and fundamental industrial medical research."

According to several proposed plans, graduate work should include, as an essential, in-plant service or residency. One large industry's in-plant fellowship program, conducted with the co-operation of a leading medical school and said to be the first of its kind in this country, was described.¹¹⁰ In most of the graduate courses now offered, "a major defect

is the lack of opportunity to give an adequate on the job experience."¹⁰⁷

In the undergraduate curriculum, Kronenberg¹¹¹ finds that "industrial medicine must be introduced and expanded if medical education is to be progressive and useful and meet present-day needs." Certain groundwork material can be introduced by "infiltrative tactics" in preclinical departments, Goldwater¹¹² stated, but industrial medicine, if regarded as a specialty, "obviously calls for special graduate or postgraduate training." He suggested that schools of public health were appropriate centers for training industrial physicians, as well as industrial nurses, engineers and chemists, and cited the inauguration of such a program at Columbia University. Among the nation's nine schools of public health, courses in industrial health and opportunities for advanced specialization in the field are generally provided.¹¹³

A crucial factor in the solution of the educational problem is the lack of established standards. Some progress was shown in the fact that residencies in the specialty of occupational medicine have been placed on a formal basis comparable to other residencies in line with the plan adopted by all certification boards.¹¹⁴ The chief difficulty remaining is to obtain suitable applicants and establish the fellowships themselves. From the viewpoint of the prospective candidates in the field of industrial medicine

both inducement and financial means were seen to be lacking.¹¹⁵ The failure of the medical profession to dignify industrial medicine with official recognition as a specialty was considered a deterrent to students in deciding to enter the field. Scholarship and fellowship funds are being established, and industry itself has been urged to subsidize graduate training.¹¹⁶

MEDICAL SERVICES

Marked inequalities persisted in the medical services provided for industrial workers in different localities and from one industry to another. In general, in-plant medical services were maintained and continually improved upon by large industries, but were still inaccessible to small industries. To what extent this disparity affects the whole picture can be judged by the fact that small concerns are estimated to constitute 99 per cent of the nation's industrial plants,¹¹⁷ employing about 60 per cent of the total labor force.¹¹⁸

No country-wide studies of the situation were reported on, but several surveys of limited groups of representative plants were made. One such study of 565 plants employing 500 or fewer workers showed that only a few provided even a minimum of medical care.¹¹⁷

In Illinois it was found that more than 12,000 small industrial establishments had no medical service,¹¹⁹ whereas in Connecticut,¹²⁰ 1400 plants employed a total of 119 physicians.

Diverse approaches to the small plants' health problem were recommended. In France¹²¹ small businesses affiliate to form a joint medical unit, a system successfully tried in one Pennsylvania community.¹²² Management-labor "safety committees"¹²³ have been organized in industries of all sizes in Sweden and also have functioned satisfactorily in some small or medium plants here.¹²⁴ In one plant of less than 1000 employees a single, full-time male nurse effectively directed the combined health, safety and welfare departments.¹²⁵ Regional programs were instituted, mostly advisory in character, in various centers such as Chicago¹²⁶ and Washington, D. C.,¹²⁷ and in areas of Wisconsin,¹²⁸ Indiana¹²⁹ and Nebraska.¹³⁰

A total of 58 industrial-hygiene units were functioning under the Industrial Hygiene Division of the United States Public Health Service, with 43 per cent of the budget deriving from state and local funds and the remainder from federal funds.¹³¹

Among new types of service reported from abroad was that in Manitoba, Canada.¹³² An industrial-hygiene bureau, operating in a comparatively thinly populated region, attempted to improve the health conditions in small plants and conducted a program featuring portable x-ray equipment, plant surveys and stipple-cell counting service. For railway workers in France, four trains fitted with x-ray apparatus were traveling all over the country and

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

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CASE 35131

PRESENTATION OF CASE

A thirty-six-year-old woman, a clerk, entered the hospital with a chief complaint of increasing constipation.

Six years prior to admission, because of right-lower-quadrant "gripping" pain and abdominal signs (details unknown), she had an exploratory laparotomy, with excision of a right ovarian cyst and a normal appendix. For two years following this procedure she was asymptomatic, but then the right-lower-quadrant pain began to recur several times a week. Two years before admission she began to notice midsacral pressure discomfort at the time of her menstrual periods, with partial relief by bowel movements. During the year before entry she had occasional sharp left-lower-quadrant pain with her menses. One and a half years before admission, for a period of five days, she had very black vaginal bleeding followed by her usual menstrual flow, and four months later three episodes of vaginal bleeding in one month. Otherwise, the menstrual periods were regular, occurring every twenty-four to twenty-six days and lasting five days, with a normal quantity of flow containing some clots. For two years prior to admission she was increasingly constipated, except that at the time of the menstrual periods, the stools were very loose and occasionally quite dark, but never black or bloody. She had some mild gaseous indigestion, without specific food intolerance or relation to meals. There was no anorexia or weight loss, and the system history was not remarkable. During the year and a half before admission three barium enemas were done elsewhere. The last two of these examinations allegedly showed a polyp in the sigmoid.

Her mother had diabetes and a mastectomy (diagnosis unknown) had been performed.

Physical examination disclosed a normally developed and well nourished woman in no discomfort. There was a well healed right-lower-quadrant paramedian scar. To deep pressure there was tenderness in the right upper and both lower quadrants, with the maximal tenderness in the right lower quadrant.

The sigmoid was palpable in the left lower quadrant and was moderately tender. There was no distention, and peristalsis was normal. Pelvic and rectal examinations were entirely negative.

The temperature, pulse and respirations were not remarkable. The blood pressure was 110 systolic, 70 diastolic.

The urine examination was negative. The hemoglobin (photoelectric-cell technic) was 14.5 gm, and the white-cell count was 7500. A blood Hinton test was negative. A barium enema demonstrated a rounded, filling defect, 2 cm in diameter, in the sigmoid at the junction with the descending colon.



FIGURE 1

The bowel in the immediate vicinity of the defect was smooth in contour, and the lumen was narrowed (Fig 1 and 2). There was some suggestion that with pressure, a change in the defect could be produced. Following evacuation, air was injected into the large bowel in an attempt to disclose any other polypoid defects. No other definite masses were made out, although at about 8 cm from the lesion described there was a questionable defect, about 5 mm in diameter, in the bowel that was partially outlined with barium. The remainder of the colon was not unusual.

After preparation with sulfasuxidine by mouth, an operation was performed on the fifth hospital day.

DIFFERENTIAL DIAGNOSIS

DR CLAUDE E WELCH: May we see the x-ray films?

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the colon was done in this patient. Whether or not a hysterectomy should have been done as well would have to be determined by the findings at the time of operation.

DR LELAND S. MCKITTRICK. Dr Welch has been very logical as well as practical in his reasoning. Dr West, the resident, also made a preoperative diagnosis of endometriosis on this patient. When the abdomen was opened I did not know what it was. I thought it was carcinoma. The lesion was just as hard as it could be. It had a characteristic appearance in the gross of a small, constrictive, scirrhous type of carcinoma, with an epiploic appendix adherent over the top of it. During the course of the resection Dr Risley, who was helping me, called attention to a small nodule along the bowel, about 6 or 7 cm from the primary lesion. This was a whitish, hard area, probably 3 mm in diameter, which looked for all the world like a carcinomatous implant. It did not have the color that one associates with an endometrial implant, and that led us to think that this was probably carcinoma rather than endometrioma. So we broadened the amount of bowel we took out. We took out more bowel than I would have taken out if I had been confident of the diagnosis when we operated because I honestly thought that we were dealing with carcinoma of the sigmoid. The patient did have a cystic tumor or mass, about 6 cm in diameter, on the left ovary that no one had felt prior to operation. She did not relax too well, I think that would have been felt if she had been examined under anesthesia or had relaxed well.

CLINICAL DIAGNOSIS

Carcinoma of sigmoid

DR WELCH'S DIAGNOSIS

Endometrioma of sigmoid

ANATOMICAL DIAGNOSIS

Endometriosis of sigmoid

PATHOLOGICAL DISCUSSION

DR CASTLEMAN. The lesion that Dr McKittrick described in the upper sigmoid presented on the serosa as a puckered, white, constricting process, which on section was seen to extend deep into the muscularis. It was grayish white and fibrous rather than granular as is seen in carcinoma. The mucosa over it was normal. The lesion measured about 3 by 2 by 1 cm, and microscopically was characteristic of endometriosis.

The microscopical section (Fig 3) showed how deep the endometrial glands had extended into the muscle layers. In a few foci the process was very close to the mucosa. A few centimeters above this lesion was another smaller one, which corresponded to the upper defect seen on the roentgenogram. There are, as Dr Welch stated, some surgeons who

believe that even if the patient is known to have endometriosis, the bowel should be resected in the presence of obstruction. Three years ago at these exercises in the discussion of a case of endometriosis, I made the statement that when endometriosis involves the sigmoid, resection has often been necessary.* Dr James R. Miller, of Hartford, wrote in and questioned the need for resection of the bowel for endometriosis, believing that castration would produce regression of the sigmoid lesion. I agree that this probably would occur in some cases,



FIGURE 3 Photomicrograph of Sigmoid, Showing Endometriosis in the Muscularis Close to Edematous and Fragmented (Artifact) Submucosa

but in a case like this, with the disease extending so deep, it may be too late. Then there is the point that Dr Welch makes that after the menopause the lesion may constrict even more.

Have you had any experience with that, Dr McKittrick?

DR MCKITTRICK. The first one I did was on a woman sixty-five years old. I do not believe the ovaries were doing much functioning, and she was operated on because she was obstructed. But going back to the case we are discussing, I believe that if I were in this woman's place I would rather have ovarian tissue and have had a segment of bowel resected than to have the bowel not resected and be sterilized at thirty-six years of age.

DR CASTLEMAN. As long as you could do an end-to-end anastomosis.

DR MCKITTRICK. That is correct. This patient had not had much discomfort. She was only thirty-

*Case Records of the Massachusetts General Hospital (Case 3221) *New Eng J Med* 235:199-201, 1946.

DR STANLEY M WYMAN On all the films there is a constant, round, smooth defect overlying the brim of the pelvis in the wall of the ascending colon, near the junction of the sigmoid. This filling defect appears perfectly smooth, and there appears to be a preservation of the mucosa over the lesion. On some of the spot films it has a suggestion of a hook, proximally and distally, that we see with intramural, extramucosal lesions. This film has a suggestion of a small, less definite mass just above the primary mass on the opposite wall of the bowel, but it is not well seen on all films, although it is seen on this large film of the colon. I should prefer to call this



FIGURE 2

an intramural extramucosal mass rather than a polypoid tumor of the colon, although one cannot be entirely certain.

DR WELCH I think the discussion of this case will be more interesting if I make a diagnosis first and then attempt to support it by the data we have. This ought to be an endometrioma of the sigmoid. If it is not, it still should be.

Let us go back over the history to see whether we can substantiate that diagnosis. At operation six years before entry a right ovarian cyst and a normal appendix were excised. Two years thereafter the patient was asymptomatic, but then the right-lower-quadrant pain began to recur. The next question arises, Could the pain have been associated with the lesion now discovered in the sigmoid? I am inclined to think that it was not pain in the right lower quadrant associated with sigmoid disease. This type of pain has been described frequently,

but the right-lower-quadrant pain from primary sigmoid disease is usually due to distention of the cecum from a constricting lesion in the sigmoid or from a contiguous, inflammatory spread from an inflamed sigmoid that has prolapsed over into the right lower quadrant. There is no evidence of distention or inflammation of the bowel, and so I assume that there was something else in the right lower quadrant. She may have had excision of an endometrial cyst at the first operation, with retention of a portion of the ovary, and again some endometriosis had developed in the remaining portion. It is surprising to find that she did not have more menstrual pain, this would indicate, if this diagnosis is correct, that endometriosis in the pelvis was not terribly extensive. The black bleeding suggests that she had adenomyosis of the uterus as well.

I assume that a proctoscopy was done and was negative.

DR BENJAMIN CASTLEMAN That is right.

DR WELCH I assume that there was no actual bleeding from the rectum at the time of the period. That might be of interest to know. Endometriomas rarely involve the mucosa, but occasionally do, with bleeding by rectum. The defect in the sigmoid on x-ray examination is perfectly compatible with this diagnosis. We have had in this hospital several lesions in the lower descending colon or upper sigmoid at this level that have been endometriosis. Interestingly enough, some have not become symptomatic until after the menopause. I suppose the increasing fibrosis that takes place after atrophy of the endometrial tissue produces obstruction. This lesion can be assumed to be still active, and the increase in symptoms at the time of the periods is explained by the congestion that occurs in the tumor. Endometriomas in the gastrointestinal tract are found chiefly in the sigmoid or on the surface of the appendix and very rarely in the lower ileum or cecum. The position of this lesion is consistent. The negative pelvic examination indicates that disease in the other pelvic viscera is minimal.

I imagine the surgeon on entering the abdomen was confronted with a minor amount of endometriosis in the ovaries, a small segment of remaining right ovary and a lesion in the sigmoid, about which it was impossible to tell the exact nature. The statement has been made in the literature that when endometriosis is the diagnosis the patient should preferably be treated by sterilization, after which the lesion will atrophy and the dangers of bowel resection will be avoided. That, I assume, was not carried out in this case for two reasons. In the first place, no one knows what the lesion is, and even if atrophy of the endometriosis did occur, there is so much involvement of the sigmoid that it is likely to progress to obstruction later on. Consequently, I assume that a resection of

The diagnosis of gastric ulcer was not sustained when a probably adequate examination of the stomach was made. A duodenal lesion was demonstrated after admission to the hospital. Therefore, we can put a question mark against the original suggestion of gastric ulcer. If he did not have gastric ulcer, which always means that the ulcerating lesion may be cancer, we can focus our attention on the biliary tract as the basis of the symptoms three months before admission. The x-ray film, which I have not seen but would like to see shortly, was certainly entirely consistent with biliary disease. He could have had a stone either in the gall bladder — with a resulting gall-bladder infection and an acute cholecystitis, in addition to a cholangitis — or in the common duct with a ball-valve action and jaundice with an attack. That diagnosis is tenable only to a certain point and may fail to explain what subsequently happened. He had lost 26 pounds in weight in the presence of diminishing jaundice. As far as I can tell from the history, there was no particular pain or discomfort associated with it. He did not vomit. There is no explanation given for this loss of weight, but it is a striking fact observed over a relatively short period. If he had had fever, one could explain the loss of weight on that basis. Certainly, an attack of biliary colic due to stone three months previously should not produce a 26-pound weight loss, without continuous or added symptoms.

Physical examination again directs attention to the biliary tract, and the statement is made that several examiners felt a tender, firm, smooth mass. It is not said whether the mass was lobular or round, which one would like to know. The mass was felt in connection with the liver below it. It moved with respiration, and everyone thought it was a palpable gall bladder. A palpable gall bladder in the absence of jaundice immediately following an acute attack of biliary colic can be due to hydrops with stone in the ampulla of the cystic duct. It very frequently occurs as a transitory phenomenon, present for a few hours and then disappearing as the stone moves. A gall bladder palpable three months after the only attack of biliary colic probably should be explained on some other basis. This is not a good example of Courvoisier's law in the sense that it cannot be described with painless jaundice. The jaundice nearly disappeared, and there was no pain for three months. He had

not had anything else for three months. The jaundice was out of the picture except at a minimal degree. At the present time one can at least invoke Courvoisier's law and try to play with it a bit in this sense. Here was a patient with a palpable mass thought to be gall bladder, and he had jaundice. That should mean ordinarily a pathologic gall bladder and obstruction at the ampulla of the common duct. That is the real meaning of Courvoisier's law. Usually the obstructing lesion is cancer of the head of the pancreas or of the ampulla or of the bile duct. The burden of proof is usually on the man who says it is not carcinoma. Rarely, we do have a palpable gall bladder in the presence of jaundice due to common-duct stone. It is very uncommon, although we have a few cases as every hospital has.

In this case there may be plugging of the duct due to a growth. There may be external pressure, let us say from a malignant lesion, which is causing marked lymphadenopathy with obstruction of the common duct at a certain level. The evidence that he had infection in the liver itself, I would say, is negligible. He could have had pain and jaundice with acute epidemic hepatitis. That is fairly common. The jaundice could persist for three months, but he should not have had a palpable gall bladder, and the liver-function tests should not have been as described in this case. He should have had a high cephalin flocculation, high thymol turbidity and a low white-cell count rather than a high one, and the differential should not have been normal. It does not seem logical to interject that possibility into the picture at all. Therefore, it seems to me that we have a right to consider one of two things without observation of the x-ray films at the moment: either a gallstone with or without a stone in the common duct, which I think is relatively unlikely, or a malignant lesion in the region of the ampulla of Vater, in the pancreas, in the ampulla itself, in the bile duct with gradual spread to the adjacent areas or even in the gall bladder.

My own belief at this stage is that the patient had neoplasm in the neighborhood of the ampulla as well as gallstones, and I am sure he ought to have been explored on the basis of this protocol alone.

I should like to see the x-ray films. They can modify the diagnostic possibilities but not the approach that should be taken.

DR JOSEPH HANDELIN: The initial examination, a cholecystogram, shows a nonfunctioning gall

six, and her right ovary and tube had been taken out. She was young, I think, for one to go ahead and do a complete castration job unless it had been necessary to do so. It seemed to me that if she progressed along reasonably well, the longer a definite operation was postponed the more freedom we would have to do the thing when it had to be done. She has convalesced and gone home.

CASE 35132

PRESENTATION OF CASE

A fifty-year-old man was admitted to the hospital because of jaundice and a weight loss of 26 pounds.

Three months before admission he had an attack of severe, sharp, right-upper-quadrant pain, radiating to below the right scapula. This pain was crampy and was accompanied by distention. He was hospitalized and in the course of a few days became jaundiced. X-ray films at this time are said to have shown a nonfunctioning gall bladder and a gastric ulcer. In the two months preceding admission to this hospital the intensity of the jaundice gradually decreased. He lost 26 pounds in weight during this period.

The patient had had indigestion relieved by either food or water since boyhood. Twelve years before admission a perforated duodenal ulcer was sutured, and since then he had followed a strict dietary regime. He continued to have "ulcer pains," but there had been no hematemesis or vomiting. Eight years before admission he was hospitalized for "stoppage of the bowels" relieved by laxatives and enemas.

Physical examination showed faint jaundice still present in the scleras. The heart and lungs were normal. There was a smooth, firm, tender, movable mass, about 3-4 cm in diameter, in the right upper quadrant, which descended with respiration. This was thought by all the examiners to be the gall bladder. The liver was not palpable.

The temperature, pulse and respirations were normal. The blood pressure was 130 systolic, 90 diastolic.

Examination of the urine revealed a specific gravity of 1.022, a + test for albumin, negative tests for sugar and diacetic acid and a +++ test for bile. Examination of the blood disclosed a hemoglobin of 12.2 gm and a white-cell count of 13,300, with a normal differential. The nonprotein nitrogen was 23 mg per 100 cc, and the total protein 7.35 gm (albumin-globulin ratio of 1.8), the serum bilirubin was 4.1 mg per 100 cc direct and 4.6 mg indirect, and the alkaline phosphatase 28.9 mg. A cephalin flocculation reaction was + in twenty-four and ++ in forty-eight hours, and the thymol turbidity 3.0 units. A blood Hinton test was nega-

tive. A gastric analysis showed free hydrochloric acid and a negative guaiac reaction.

A Graham test demonstrated failure of the gall bladder to fill. In the right upper abdomen there was a dense calcification, 1.0 cm in diameter, that was consistent with a stone in the gall bladder or common duct or mesenteric lymph node. A cluster of calcifications, probably in the pancreas, was also noted. A barium enema was negative. A gastrointestinal series was done. The stomach was pliable, and its mucosal pattern within normal limits. The patient permitted little palpation in this region, but no ulceration or filling defects were demonstrated. The duodenal bulb was deformed in a manner consistent with previous surgery. There was an irregularity of the lesser curvature and of the duodenal loop about which no opinion was given.

On the eighth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR CHESTER M. JONES. This is the sort of case in which a precise diagnosis is interesting but unimportant. The important thing is the decision what to do, and the sooner that decision is made, the better. One may make an intelligent guess that is logical but a mistaken diagnosis. The past history was that of ulcer with perforation twelve years before admission. The perforation was probably closed successfully. The duodenal-ulcer problem remained. Closure does not solve that problem at all. The episode eight years prior to admission, which was called intestinal obstruction and which responded easily to simple methods and did not recur, is not pertinent to the present discussion. The subsequent history of prolonged change in the bowel habit, I judge, was due to fecal impaction.

That leaves us with a man of fifty years with a three-month history initiated by right-upper-quadrant pain, which is in the classic location for gallstone colic. The pain radiated through to the right scapula, following which he was jaundiced. On the basis of the story alone and in the absence of other demonstrable facts, there is no reasonable doubt that he had biliary colic. The fact that a gastric ulcer was said to have been demonstrated at this time is interesting, but it is hearsay evidence. It may have been a faulty interpretation. It would not be the first time that a gastric deformity, even one that persisted for an unusual period, was not found at exploration, but at operation gallstones were present. In other words, for some reason or other, gall-bladder disease associated with stones can occasionally produce a constant gastric deformity that is indistinguishable from cancer or ulcer. It is very uncommon but it does occur, and I can think of several important cases here in which the diagnosis prior to operation was gastric cancer and at operation we found only gallstones.

seeped in, which surely suggests disease of the gall bladder

CLINICAL DIAGNOSES

Cholelithiasis, with common-duct stone

Peptic ulcer

DR JONES'S DIAGNOSES

Gallstones

Cancer of biliary tract, probably of bile duct

ANATOMICAL DIAGNOSES

Adenocarcinoma, Grade II, of head of pancreas, with metastases to peritoneum, liver, gall bladder, regional lymph nodes ileum, stomach and lung

Chronic pancreatitis

Ascites

Common-duct stone

Cholecystgastrostomy, recent

PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY At exploratory operation the peritoneal cavity was immediately found to be studded with cancer metastases, as was the surface of the liver. Because of adhesions in the region of the stomach and duodenum, it was impossible to carry out an extensive exploration, but the surgeon was under the impression that the head of the pancreas felt like cancer and on that basis did a cholecystgastrostomy.

DR JONES Did he describe the gall bladder?

DR MALLORY It was distended. It is not stated to what degree, however. The patient lived only four weeks after operation. At the time of autopsy we found extensive cancer of the head of the pancreas and also very extensive chronic pancreatitis involving all the rest of the organ and, I think, explaining by means of fat necrosis the calcification that the x-ray examination showed in the body of the pancreas. There was a stone in the common duct a few centimeters up from the ampulla, as Dr Jones predicted. The ampulla was quite free, for when the stone was removed, the common duct opened unobstructed into the duodenum. The jaundice, I believe, was due to the gallstone, not to the carcinoma. Between the time of operation and the autopsy the tumor had extended to some extent and now involved the serosa of the gall bladder and the stomach but was evidently not primary in either place. We could not find any trace of the old duodenal ulcer.

DR JONES Was the liver enlarged particularly?

DR MALLORY Slightly, not greatly.

DR HANELIN Was there any fluid in the lesser peritoneal sac?

DR MALLORY About 500 cc in the general abdominal cavity, not in the lesser peritoneal space. There was a small, fluid-filled area immediately adjacent to the midportion of the pancreas in the retroperitoneal tissues. It contained only 30 cc of fluid. There were also some carcinomatous implants on the serosa of the stomach.

bladder and a calcium density, 1 cm in diameter, in the upper abdomen. In addition, there are multiple punctate calcifications, which extend from the right aspect of the second lumbar vertebra upward and to the left. These are very likely pancreatic calcifications. The larger calcified density in the upper abdomen is seen to overlie the spine and may represent a stone that had its origin in the gall bladder. It is situated somewhat higher and more medial than the usual position of the gall bladder so that it might be within the cystic or common duct.

DR JONES It is fairly high to be in the ampulla, it is at the first vertebra, is it not?

DR HANELIN Yes

The barium enema shows no evidence of intrinsic or extrinsic colonic abnormality. There is an interesting shadow visible in the right upper abdomen, which may be of importance. It is superimposed upon the liver and kidney and may represent the clinically palpable mass. Films of the upper gastrointestinal tract show no intrinsic abnormality of the stomach. The duodenal bulb, however, is deformed in a manner characteristic of chronic ulcer.

DR JONES In addition to the effect of surgical operation

DR HANELIN It is difficult to be certain to what extent surgery contributes to this deformation. The second portion of the duodenum is displaced toward the midline and is indented along its lateral aspect. There is also a suggestion of a smooth pressure defect along the lesser-curvature aspect of the stomach.

DR JONES It could be the left lobe of the liver.

DR HANELIN Yes, that is its usual location.

DR JONES In other words, there is no evidence of a gastric lesion, which I think is of some importance. There is an abnormality here that has to be taken into account. It could be a gallstone that would have to be in the upper part of the common duct or, as Dr Hanelin said, in the cystic duct near its junction but not near the ampulla. It would be high for that. This is the region of the first lumbar vertebra, and usually the ampulla is at the junction of the second and third lumbar vertebrae. Is that correct?

DR HANELIN That is correct. A tumor of the head of the pancreas, if large enough, should en-

croach upon the second portion of the duodenum from its inner aspect.

DR JONES In addition, something of interest that does not help in the diagnosis is the appearance of the fine calcification in the region of the body of the pancreas. It may well be pancreatic calcification. It does not explain the entire history to me, although calcification of the pancreas may be associated with repeated attacks of pain, jaundice, fever and loss of weight. To be sure, this is the first attack, but I doubt very much if we could do more than say that there may be some disease of the pancreas that has caused calcification but is not the cause of the symptoms. In my mind, it has no significance as far as the presence or absence of cancer is concerned. If I understand Dr Hanelin correctly and interpret these films correctly, there is no evidence of involvement of the duodenum by compression from a cancer of the pancreas.

DR HANELIN That is correct.

DR JONES The duodenal loop is not compressed from the inner side, suggestive of pancreatic disease. It might suggest something external to the duct or absolutely contiguous with the duct, possibly arising there or within the gall bladder. I should say that the suggestion that Dr Hanelin made that there is some pushing of the duodenum toward the midline is much more evidence of tumor. It does not give any idea of the nature of the tumor. Therefore, I am left where I was before I saw the x-ray films. I believe he had a gallstone and some other disease in addition. I do not believe that pancreatitis alone will explain it. I would expect to find cancer, probably of the duct itself or of the ampulla, possibly of the gall bladder. I should be very much surprised if he had only stones in the common duct and nothing else. He certainly should have been explored in the hope that that might be the case and, lacking that, in the hope that cholecyst-enterostomy of some sort might permit palliation of a more serious condition and possibly resection of the tumor.

The other thing I did not comment on was the second x-ray finding of a nonfilling gall bladder. With jaundice it is not surprising that the gall bladder did not fill. With diminishing jaundice the result of the second Graham test should have been anticipated. Nothing was said about the stools. If bile were going through, some dye might have

bones of contention. The other two strike closer to the meat of the matter.

One alleges that Dr. Van Waters failed to provide the prisoners with good examples by hiring former inmates as staff members. The Board called the charge "irresponsibly made" and added: "The example afforded by such persons, showing that it was possible to make good despite handicaps and errors, could be an important factor in the rehabilitation of other inmates."

The fourth, and possibly the most significant, group of charges accused Dr. Van Waters of violating state indenture laws by allowing inmates to be employed in other than domestic capacities. These laws were drawn up some seventy-five years ago. They specified that prisoners could work only as domestic servants. Since there were extremely few occupations open to a working woman in the 1870's, those laws are now inordinately restrictive. The board found that a fair amount of leeway in this respect had been allowed by former commissioners. It decided that the responsibility was theirs.

Commissioner McDowell once commented, "There can't be one law for great penologists and another for the rest of us." True enough. But laws are seldom changed until someone is courageous enough to test them and find them wanting. In a progressive society the letter of the law ever lags behind its spirit. Often enough, those who adhere too strictly to statutes whose origins are fundamentally humanitarian are left groping in the backwash of progress with nothing to guide them but a dusty law book.

Clearly, Dr. Van Waters is ahead of the law. She has no use for the punitive aspects of prison life. She believes that enforced incarceration as an end in itself embitters more than it educates.

She calls her charges "students." Their troubles receive psychiatric attention, and the institution officers are their confidantes. They were encouraged to seek gainful employment in occupations of their choice and in line with their talents. Her entire program was geared to the principle of preparing the inmate for a successful return to the community.

She and others should be allowed to proceed on this principle. Nothing in the law should impede the temperate operation of the methods she has done so much to advance. Salaries should be raised

to attract more persons of Dr. Van Waters's stature (both as institution heads and as commissioners of correction). The responsibilities of prison heads should be more clearly defined. The indenture laws should be liberalized. Even use of the term "indenture"—with its implications of bondage—might well be abandoned.

Let society catch up with Miriam Van Waters! That is indeed a challenge.

NEW PROGRAM IN PHYSICAL MEDICINE AT COLUMBIA

IN MAY, 1944, Bernard Baruch made a grant of \$400,000 to Columbia University to aid in the development over a ten-year period of a model center for teaching and research in physical medicine as recommended by the original survey by the Baruch Committee. Under the guidance of a committee on physical medicine of the medical faculty this project developed with signal advance in the therapeutic application of physical medicine, particularly including rehabilitation, and in education of technicians in physical and occupational therapy and of physicians training to specialize in the field. Some important basic research particularly in physiology has also been instigated.

This program has enlarged to such an extent that it includes the Columbia Presbyterian Medical Center, the Institute of Crippled and Disabled and eight other hospitals in New York City. In 1947 nearly 200,000 physical-therapy and occupational-therapy treatments were given in the medical center alone. To keep pace with this growth a new program has been announced by President Dwight D. Eisenhower. Dr. Robert C. Darling, associate professor of medicine at the College of Physicians and Surgeons, will serve as co-ordinator of physical medicine and rehabilitation, as well as director of research, a post he has filled for the past three years.

With the world-known rehabilitation facilities of the Institute of Crippled and Disabled and the wealth of clinical opportunities at Presbyterian and affiliated hospitals, together with a well co-ordinated research program, one should indeed anticipate at Columbia a model center for training and research in physical medicine.

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JUSTICE AND THE LAW

IN SCIENCE as in sociology the words of St. John "And ye shall know the truth, and the truth shall make you free," have particular significance, for on them depends the direction in which mankind will move during the coming years. Massachusetts has now on the record two recent celebrated cases the final outcome of which will depend upon the degree to which truth can be served.

The first of these, the stand of the medical profession against the antivivisectionists, although still unsettled, has already spotlighted certain aspects of scientific progress. The second, Dr. Miriam Van Waters's fight for reinstatement as head of the Framingham Women's Reformatory, will, it is hoped, have educated the public in the ways of humane and progressive penology.

It is regrettable that public scrutiny should have been fixed on Dr. Van Waters's methods in such an atmosphere of malicious sensationalism. Whatever their motives in bringing the twenty-seven preposterous charges of "misconduct in office" against one of the foremost sociologists of our time, it seems evident that Commissioner of Correction Elliott E. McDowell and possibly others in penologic and political circles had a score to settle with Dr. Van Waters. Fortunately they failed, she stands completely vindicated, and her accusers are utterly discredited.

Parenthetically it may be added that not so many years ago Massachusetts lost the services of another able penologist, Howard B. Gill, who was ousted as head of the Norfolk Prison Colony, where McDowell was supervisor of workshops before he became commissioner last year. At that time, however, there was no state law giving public officials the right of appeal. Howard Gill stayed fired.

Dr. Van Waters served happily and successfully under five commissioners for sixteen years before McDowell was appointed. She filled well the shoes of such enlightened predecessors as Clara Barton and Mrs. Jessie Hodder. Her work has made Framingham one of the most studied and emulated penal institutions in the world.

Three months after he assumed office McDowell ordered the investigation of the reformatory. He had already indicated his hostility to her methods. The tactics employed during the inquiry were questionable. The charges revealed the spite and lack of vision of her accusers. They may be divided roughly into four categories, two of which may be dismissed without discussion.

One comprises accusations that Dr. Van Waters failed to stop sexual perversion among inmates. The review board appointed by the Governor found that everything possible had been done to contain a problem that exists in every situation where the sexes are segregated. The other includes a grab bag full of picayune charges, none of which were found to be just cause for removal.

These two groups of reasons seem to have been simply an attempt to justify the dismissal. They have little bearing on what appear to be the main

amply demonstrated by the sad fate of the Nazi Medical Corps, and there can be no quarrel with the deferment of men already embarked on a medical career. Whether we are fated to live through a long cold war, another hot war or no war at all, they will be needed. It was presumably at this point in their thinking that National Headquarters issued Memorandum No 7.

But thinking need not stop there. The question is not the deferment of medical students but the deferment of "premedical" students. Granted that medical training is long, will a college freshman who is eighteen months older for having done his military service be, for that reason, deterred from following the career for which he believes himself best fitted? And, more important, can an eighteen-year-old boy be counted on to evaluate maturely his motives for calling himself "premedical" and accepting draft deferment? Certainly a youthful desire to escape the draft would be an inadequate and unfortunate motivation for the support of a life-long career in medicine—a career, by the way, that will not and should not exclude the possibility and the duty of later military service.

The decision arrived at by the Harvard Faculty is surely foresighted and sound, and it is hoped that a similar clarity of thought and sincerity of purpose will guide the rest of the medical faculties in resolving the serious issue that Memorandum No 7 has placed before them.

MASSACHUSETTS MEDICAL SOCIETY

TREASURER'S REPORT COVERING REFUND DISTRIBUTION

The Treasurer of the Massachusetts Medical Society makes the following report regarding the refund to the district societies for 1949.

The Council voted to distribute the sum of \$8000 00 to district societies. The total number of payments of annual dues received by the Treasurer by March 1, to be counted for the refund, was 4647. Therefore, the refund to the district societies for each paid fellow is \$1 72.

The following table gives the number of payments, as of March 1, and the refund to each district as of March 9.

DISTRICT	NUMBER REPORTED PAID	REFUND
Barnstable	44	\$76 07
Berkshire	126	217 12
Bristol North	60	103 59
Bristol South	197	339 24
Essex North	181	311 72
Essex South	254	437 28
Franklin	45	77 79
Hampden	298	512 96
Hampshire	72	124 23
Middlesex East	132	227 44
Middlesex North	125	215 40
Middlesex South	936	1,610 32
Norfolk	870	1,496 80
Norfolk South	140	241 20
Plymouth	140	241 20
Suffolk	577	992 84
Worcester	562	625 04
Worcester North	88	151 76
	4,647	\$8,000 00

In 1948, for comparison, the total number of payments for the refund was 4541.

ELIOT HUBBARD, JR., M.D., *Treasurer*

THE \$25 00 ASSESSMENT

On March 1, 1949, I sent the American Medical Association \$50,000 as the first installment of the contribution of the membership of the Massachusetts Medical Society to the Campaign of Education. This represents payment of the assessment by about a third of our members. The checks are coming in to this office every day in a rather constant flow. One thousand checks were received within two weeks after the bills were mailed.

A description of the method we used here was sent to the other New England states and I have received word from them that they are all co-operating in this effort. The Washington State Medical Association has made the assessment compulsory, and I know of no other state society that has done so. Some states have increased their own dues for this public-relations effort. Michigan has done this for four years and has accumulated a fund of \$400,000 to use in educating the public in that state concerning the nation's health.

I have received some checks for more than \$25 00. A few checks have been for less than the amount asked because of personal financial difficulties. Only 12 fellows have written to say that they will not pay. Many more letters have been received praising this worthy effort.

It is my hope that by the end of March we shall have received checks from nearly 100 per cent of our members.

H. QUIMBY GALLUPE, *Secretary*

Dr Darling, the new co-ordinator, a graduate of Harvard Medical School, served as assistant director of the Fatigue Laboratory at Harvard and also as a consultant to the Quartermaster General. His studies have particularly dealt with various aspects of physical fitness, and he recently rendered a report on this subject in the *Journal of the American Medical Association* as chairman of the Baruch sub-committee on physical fitness. The organization of such a strong program in physical medicine at Columbia should attract competent young physicians into this rapidly growing and important field of medicine.

CANCER OF THE LUNG

OVERHOLT and Schmidt, in their paper on survival in primary carcinoma of the lung, delivered at the annual meeting of the New England Surgical Society last October and published elsewhere in this issue of the *Journal*, have made a valuable contribution to the increasing knowledge of cancer.

Improvement in the operability rates and in the operative results are encouraging but are to be expected, particularly in a branch of surgery that has been so recently developed as has been surgery of the lung. Less encouraging and presenting, indeed, a distinct challenge to both medical practice and medical public relations is the time that still elapses between the first symptom experienced by the patient and the establishment of the diagnosis.

This tragic interlude averaged eleven and three-fourths months for 133 patients who were seen between 1932 and 1942. Three months elapsed before the patient visited the doctor, another three months passed by before the first x-ray examination was made, and still another *five and three-fourths months* were lost before the diagnosis was made. Since 1942 this long interval has been reduced only to ten months. The doctor is now not consulted for three and eight-tenths months, the first x-ray examination is made one and six-tenths months later, and four and six-tenths more precious months elapse before the diagnosis is established.

This total interval can conceivably be completely eliminated by the same type of radiologic screening of the population that is now employed in tuber-

culosis case finding, for the growth can usually be discovered by the experienced radiologist or chest specialist before it begins to produce symptoms. Notice of abnormal areas of density spotted in survey films is reported back to the referring physician. It is his responsibility to see that any silent, abnormal density is properly labeled. His patient may have a silent, primary cancer of the lung, which, in most cases, is localized and can be treated successfully then, but not later.

Cancer of the lung should carry the highest rates of cure of any type of internal cancer because the time schedule of discovery can be set ahead to antedate symptoms. The responsibility is threefold: support by the laity of mass screening of the adult population on an annual basis, proper sorting of areas of silent abnormal densities by the medical profession generally, and reliance on exploratory thoracotomy in suspected cases.

UNWISE DRAFT DEFERMENT

ACCORDING to a recent release from the University News Office, the Faculty of Medicine of Harvard University has decided to continue its present policy of certifying for Selective Service deferment only students who are eligible to enter medical or dental school in the fall of the current year. Under the provisions of Local Board Memorandum No 7 of National Headquarters, Selective Service System, the faculty was empowered to certify men in their first and second years of college by regarding them as premedical students and by provisionally recording their names for admission to future medical studies. The refusal to avail itself of this power represents a wise and honest decision on the part of the Harvard faculty.

A similar decision has been reached by a few other outstanding schools, notably, Boston University, University of Cincinnati, Johns Hopkins, University of Missouri, University of Wisconsin and Yale, but the remaining medical faculties throughout the country are still undecided. The dilemma confronting them is more important than it seems at first sight.

The folly of allowing military service to cut off the supply of future doctors, even in time of war, was

amply demonstrated by the sad fate of the Nazi Medical Corps, and there can be no quarrel with the deferment of men already embarked on a medical career. Whether we are fated to live through a long cold war, another hot war or no war at all, they will be needed. It was presumably at this point in their thinking that National Headquarters issued Memorandum No. 7.

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Essex South	254	437.28
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Hampden	298	512.96
Hampshire	72	124.23
Middlesex East	132	227.44
Middlesex North	125	215.40
Middlesex South	936	1,610.32
Norfolk	870	1,496.80
Norfolk South	140	241.20
Plymouth	140	241.20
Suffolk	577	992.84
Worcester	362	623.04
Worcester North	88	151.76
	4,647	\$8,000.00

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ELIOT HUBBARD, JR., M.D., *Treasurer*

THE \$25.00 ASSESSMENT

On March 1, 1949, I sent the American Medical Association \$50,000 as the first installment of the contribution of the membership of the Massachusetts Medical Society to the Campaign of Education. This represents payment of the assessment by about a third of our members. The checks are coming in to this office every day in a rather constant flow. One thousand checks were received within two weeks after the bills were mailed.

A description of the method we used here was sent to the other New England states and I have received word from them that they are all co-operating in this effort. The Washington State Medical Association has made the assessment compulsory, and I know of no other state society that has done so. Some states have increased their own dues for this public-relations effort. Michigan has done this for four years and has accumulated a fund of \$400,000 to use in educating the public in that state concerning the nation's health.

I have received some checks for more than \$25.00. A few checks have been for less than the amount asked because of personal financial difficulties. Only 12 fellows have written to say that they will not pay. Many more letters have been received praising this worthy effort.

It is my hope that by the end of March we shall have received checks from nearly 100 per cent of our members.

H. QUIMBY GALLUPE, *Secretary*

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(Notices concluded on page xiii)

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MEDICAL MISSION TO GREECE AND ITALY

CHESTER M. JONES, M.D.*

BOSTON

DURING the spring of 1948, medical missions were sent out under the auspices of the Unitarian Service Committee to various university centers, one to Greece and Italy, one to Poland and Finland, one to Germany, and one to Colombia. The present report deals briefly with experiences of the Greek-Italian Mission, which operated under the chairmanship of Dr. Paul D. White. Like that of previous missions organized and sponsored by the Unitarian Service Committee, its purpose was to meet important medical groups at a university level in centers that had been separated by the war from sources of new information over a period of years. By means of direct contact with heads of departments and with leading practitioners, it was possible to accomplish this and, what seemed of equal importance, to re-establish professional relations that had been broken since 1938. The sponsorship of this particular mission was divided between the Unitarian Service Committee and American Aid to Greece (AMAG), the agency through which the United States is providing material aid and professional advice to that unhappy country.

To give a representative background to professional opinion, the group was comprised of men from five American Universities and one Canadian institution and represented departments of physiology, bacteriology, pharmacology, internal medicine, general surgery, neurologic surgery, oral surgery, anesthesiology and dental research. Official invitations had been received from the universities of Athens and Salonika in Greece and from the faculties of Rome, Florence, Bologna, Turin and Milan in Italy. The procedure in each center was the same—that is, immediate and direct contact with the medical faculty, a series of planned formal lectures with the aid of medical interpreters and, much more important, a series of informal meetings as well as ward rounds and visits to various hospital centers in the areas concerned. By such an approach it was possible to establish a friendly relation with key individuals and to see at close range the existing problems, not only those that affected

the teaching of medicine and the care of the sick but also the political and social ones. A great deal of information was made available through embassy officials, governmental agencies and casual conversations with medical students and civilians who were encountered in the various cities.

The situation in Greece during the April and May of our visit was extremely critical, inasmuch as the Greek Government was attempting to wage an internal war successfully and at the same time to reconstruct a country ravaged and depleted by Italian and German occupation and subsequent guerilla activities. At the time of our arrival a certain amount of stability was being obtained through the help of AMAG, which provided both military aid and advice and the actual distribution of relief to refugees and to communities in dire need of reconstruction and reorganization. From the first it was apparent that military necessities were uppermost, with the result that the needs of education and medical care were forced into a position of secondary importance. Added to this was the evident and appalling overcrowding in the schools, both in Athens and in Salonika. Although this applied to all departments of the universities, it was especially true in the medical schools, where there were approximately 4000 registered students in Athens and 2000 in Salonika. This student load imposed almost impossible difficulties in the way of adequate instruction, which at best had to be largely didactic. Besides the difficulty of excessive numbers, instruction was hampered by two factors: the relatively small number of experienced senior men, and the almost complete dearth of properly trained younger faculty members. The latter was due in part to actual losses during the war and in part to the fact that during the war years no planned, thorough training program could be maintained to provide for a sufficient number of younger men, because of the immediate and pressing necessities of care for the sick and indigent. As a result of all these circumstances, in addition to the fact that there had been little or no access to sources of current medical progress, Greek medicine was just beginning to emerge from a static phase of some years' standing.

*Clinical professor of medicine, Harvard Medical School; physician, Massachusetts General Hospital.

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(Notices concluded on page xiii)

interest was maintained and a very friendly atmosphere existed in centers where it was entertained.

An unforgettable by-product of the Greek Mission was a visit to the ecclesiastic community on Mt Athos, made possible by special permission from the Greek Government and from the ecclesiastic authorities. This community is completely isolated from the present-day world by its own, centuries-old traditions and practices. It is composed of some twenty monasteries situated on the tip of the Mt Athos peninsula. The Mission had an opportunity to see several of these monasteries, an experience of extraordinary interest because of the rich tradition of church lore and custom that went back to the period of Byzantine influence. The costumes and treasures were fascinating. Many of the monks were examined at their own request. With rare exception, these men who live an almost medieval type of life were in good physical health. Infectious disease seemed to be nonexistent, except for mild forms of endemic dysentery. Because of their extreme seclusion, psychosomatic disorders were not uncommon, but degenerative disease appeared to be at a minimum. A large number of monks were well into the eighth and ninth decades. The psychologic difficulties were noted more often in the younger monks, many of whom were obviously insecure and rather frustrated.

The effects of guerilla warfare were everywhere evident. Athens and Salonika were crowded with refugees, and really adequate nutrition for the average person was a critical problem. Sufficient food was available only for those of means, there were still evidences of wealth among a few. In Salonika, particularly, the fruits of guerilla warfare were seen at close hand. Troops and gendarmerie filled the city, and the military hospital was overflowing with recent casualties, most of which were being taken care of fairly efficiently although at times measures had to be improvised, owing to the lack of equipment and supplies. Civilian casualties were also numerous and presented a depressing sight. Periodically, guerilla forces raided outlying villages that were totally undefended and killed or maimed old men, women and children indiscriminately for no other purpose than to create terror and force evacuation of farms and villages. Survivors of these raids were occupying hospital beds and were kindly treated although under very difficult circumstances. They were frequently found side by side with unwounded children who were being temporarily housed in the hospital because of lack of other facilities. In these unfortunates the effects of starvation were obvious and distressing.

One special aspect of medical education in Greece is worthy of comment — that is, the plight of the medical student. Mention has already been made of the gross overcrowding of the schools. Following central and often western European tradition, there is no screening of medical students prior to matric-

ulation. This is one of the causes of the tremendous crowding, and as a result medical students are ill equipped for study and work. Housing conditions are poor and insufficient, textbooks and periodicals are noticeable by their absence. Student libraries exist but are totally inadequate to supply the student needs. Reading is almost entirely limited to textbooks, which are usually out of date, and consequently the difficulties imposed by restricted laboratory and hospital facilities and by the didactic method of teaching are enhanced by the impossibility of access to sources of modern medical information. A great number of the students are extremely poor, and living is almost at a subsistence level. Faculty interest in students is traditionally a distant one, although a few outstanding exceptions were encountered, where members of the faculty and their wives were trying to do everything within their power to make the lot of the student a happier one. Resident and research facilities such as are known in this country are nonexistent.

Finally, tribute should be paid to individual members of the AMAG group who were particularly interested in public health and education. Among numerous other activities, this group has been instrumental in the distribution of much-needed supplies and has gradually increased medical facilities although these are still far below optimal levels.

* * *

In Italy the work of the Mission proceeded along lines similar to those followed in Greece but at a much more rapid rate. The universities at Rome, Turin, Milan, Bologna and Florence were visited in turn. In addition to a series of formal lectures before faculties and students, interesting personal contacts were made between individual members of the Mission and their corresponding faculty members in the various cities. The transition from Greece to Italy showed sharp contrast despite the fact that Italy is far from restored to a normal level of political or social activity. Here too laboratories often evidenced the lack of many essential supplies and diagnostic equipment, medicines were absent or difficult to obtain. In the universities visited, the level of faculty activity was less restricted, and modern methods were being utilized in many instances very effectively and intelligently. Research was being carried on in individual units although under the ever-present limitations imposed by insufficient personnel and equipment. Scientific curiosity was keen in many quarters. Experienced clinical skill and awareness of the recent advances in medicine and surgery were obvious in the departments that were visited. The Forlanini Institute of Rome, for example, was a magnificent structure for the care of tuberculosis. It was thoroughly up-to-date and well equipped with ample provision for animal work and for modern therapeutic measures incident to the treatment of tuberculous

Because of depletion of scientific supplies and lack of funds for replacement, university, hospital and laboratory shelves were empty, or at best held very meager and ill balanced equipment of all sorts. Many important drugs were lacking, facilities for nursing and dietary care existed at only basic levels, and the hospital beds were filled to overflowing because of the great influx of civilian and military casualties.

The Greek medical situation has been colored of necessity by various developments in the country's history and tradition. This applies not only to the present critical situation but also to previous political, social and economic factors dating back at least to the beginning of the present Greek nation with its changing course under kings, republics and dictators. Economically poor, politically unstable and rarely organized from the point of view of efficient government, Greece has not had the opportunity to put on a firm basis sound medical traditions such as have obtained in other continental centers — in Vienna for example, where a greater degree of stability over a longer period has made it possible to establish great academic customs and advantages. The universities of both Athens and Salonika are governmental bodies, financially largely dependent on governmental grants (at present absent or completely insufficient). Appointments to the staff are in a sense political posts. Paralleling the changes in the Government, in Athens particularly, changes in faculty personnel are frequent, valuable men at times being replaced by others less capable but politically affiliated. This practice, not of course limited to Greece or even to Europe, represents a definite hazard to academic effectiveness since it leads to uncertainty of tenure of office and hence to inability to plan constructive departmental budgets, nor is the state of mind produced by such insecurity conducive to forward thinking even were other circumstances ideal.

Instruction in the medical schools, as noted above, was largely didactic, owing to the size of the classes. The clinical professors in many institutions were able, experienced physicians and surgeons, whose training reflected the teachings of the French, German and Austrian schools. Unfortunately, by tradition as well as by necessity of actual events, interest in and profound knowledge of the best in modern physiology and in the fundamental sciences was distinctly limited, although here again certain individuals stood out as men of great experience and learning. For the most part, however, teaching of the fundamental sciences was far behind what is currently demanded by modern medical concepts, and this was reflected in the therapeutic approach to disease, treatment being based chiefly on tradition and empiric knowledge rather than on physiologic and pharmacologic advances of recent years. The newer aspects of anesthesia were unknown, and consequently

present-day transthoracic surgery with all its implications was not possible. Newer drugs, such as penicillin and streptomycin, were available only in limited quantities. Furthermore, completely inadequate housing and feeding facilities rendered it impossible to care for the tremendous overload of infectious disease. Tuberculosis posed a menacing problem of great magnitude with no immediate hope of isolation of open cases or of proper therapy, although there were many physicians who were entirely capable of treating this disease under normal circumstances. To other difficulties there was added a certain amount of fatalistic apathy. This attitude, not limited to the medical profession, is the inevitable outcome of the Balkan wars and the two world wars that have harried Greece for many decades — to say nothing of the existing "civil war," which is essentially a struggle between the communistic elements, trained and supplied by outside sources, and the present rather inefficient Government. Uncertainty was in the air, particularly when the Mission arrived in Greece, although it was of extreme interest to note an ever-increasing spirit of optimism and hope subsequent to the improving military situation under American guidance and aid.

In contrast to the obvious difficulties and at times somewhat deplorable aspects of Greek medicine, certain achievements and certain bright spots stand out brilliantly. Gastric surgery in Athens was exceptionally well done. Subtotal gastrectomy was performed with a high degree of technical skill and low mortality, and experience in this particular operative procedure was great, inasmuch as the incidence of ulcer in the community, as reflected in the hospital population, was high. Echinococcal disease was extremely common, owing to the animal carriers that were completely uncontrolled by any sanitary measures, and as a result surgery of echinococcal cyst was also advanced and skillfully performed. Gynecology and obstetrics were at a high level of performance, at least in university centers, because of the outstanding work of the dean of the Athens Medical School. From the public-health point of view, the widespread and continuous campaign against malaria had borne fruit to the extent that active cases of malaria in Greece have been reduced to a few thousand instead of several million. DDT spraying by air over malarial areas has been most effective, and was the one activity that was not interfered with by guerilla groups. In spite of woefully inadequate supplies of streptomycin, treatment of tuberculous meningitis had been carried out with more or less immediate success in a small number of cases. Interest in newer methods of diagnosis and treatment was keen although frequently it was impossible for the local profession to act on information because of lack of facilities. During the entire stay of the Mission in Greece, a genuine

GASTRIC SUCTION A PROPOSED ADDITIONAL TECHNIC FOR THE PREVENTION OF ASPHYXIA IN INFANTS DELIVERED BY CESAREAN SECTION

A Preliminary Report

SYDNEY S. GELLIS, M.D.,† PRISCILLA WHITE, M.D.,‡ AND WILLIAM PFEFFER, M.D.§

BOSTON

IN THE course of a study involving approximately 500 infants born to diabetic mothers,¹ it became evident that respiratory difficulty, consisting of increased respiratory rate, cyanosis and retraction of the soft parts of the chest, was the most consistent abnormal finding in the neonatal course of these infants. These signs were frequently present at birth but also appeared several hours after birth and could not be correlated with hypoglycemia, cerebral injury or atelectasis, or with the cardiac hypertrophy that Miller² has found in such infants. The great majority of these infants had been delivered by cesarean section, it is well known that the incidence of respiratory difficulty and the mortality rate are higher in infants born by section than in those delivered through the pelvis. It therefore appeared possible that the mode of delivery was in part responsible for the abnormal respiratory signs noted in the infants of diabetic mothers. Delivery by cesarean section increases the likelihood of aspiration of amniotic fluid, and such aspiration seemed a likely explanation for the obstructive respiratory signs present immediately after birth. The aspiration of amniotic fluid during birth did not, however, appear to be an entirely satisfactory explanation for the sudden development of respiratory difficulty several hours after birth. It occurred to us that an excessive amount of amniotic fluid might be ingested at delivery and subsequently be regurgitated and aspirated, thus accounting for the late onset of respiratory embarrassment.

To test this hypothesis two series of infants of diabetic mothers were studied. All mothers received spinal anesthesia without analgesia and were delivered by cesarean section in the thirty-eighth week of pregnancy by the same obstetrician (Dr. Raymond S. Titus). All infants were observed at birth by one of us (S.S.G.), and all initial gastric suction was performed by the same person. The infants were extracted as quickly as possible to minimize the opportunity for crying or gasping before extraction of the head. The clearing of the airway and the administration of oxygen were per-

formed in a uniform manner in all infants. Gastric suction was carried out within one or two minutes of birth by means of a No. 10 French rubber catheter passed through the oropharynx. A resuscitator supplied the negative pressure for suctioning. The catheter was passed slowly down the mouth into the esophagus, with constant suction applied and with slow, rotating movements of the catheter between the fingers. When the catheter reached the stomach, gentle pressure was applied

TABLE 1 Gastric Suction in Infants of Diabetic Mothers Delivered by Cesarean Section

INFANT No.	BIRTH WEIGHT		VOLUME OF GASTRIC CONTENTS	CLINICAL COURSE
	lb.	oz.		
1	5	1½	5	Normal
2	5	11	20	Normal
3	6	1½	12	Normal
4	5	8½	14	Normal
5	6	2¼	15	Normal
6	7	1	26	Normal
7	7	14½	24	Normal
8	4	9	14	Retraction at birth, infant cyanotic and limp, retraction continued for a few hours and subsequent course normal
9	5	6	17	Retraction at birth, complaining cry, course normal on the next day
10	7	15	10	Normal
11	6	1¼	20	Normal
12	6	9½	24	Normal
13	7	5½	36	Normal
14	7	15	18	Normal
15	5	15¼	20	Slight retractions lasting 48 hours
16	6	15	20	Normal
17	7	6	24	Normal
18	9	3	15	Normal
19	10	8	20	Normal
20	5	—	35	Normal
21	7	4	18	Retraction at birth and for first four hours, remainder of course normal
22	5	2	10	Normal
23	7	7	24	Normal
24	9	—	26	Normal
25	5	2	15	Normal

over the abdomen to facilitate the greatest yield of fluid. The catheter was withdrawn slowly, still with constant suction applied. Tracheal catheterization was not carried out in any of the patients. Oxygen was then administered for approximately one or two minutes, after which the stomach suction was performed two or three more times until fluid could no longer be obtained. The infants were placed in incubators with oxygen flowing constantly at the rate of 6 liters per minute. Suction of the nares, nasopharynx, mouth and oropharynx was carried out as often as appeared necessary. After initial gastric suction had been performed, this

*From The Children's Medical Center and the Faulkner Hospital and the Department of Pediatrics, Harvard Medical School.

This investigation was supported by a research grant from the Division of Research Grants and Fellowships of the National Institute of Health, United States Public Health Service.

†Associate in pediatrics, Harvard Medical School, chief, Medical Out-Patient Department, Children's Hospital.

‡Instructor in pediatrics, Tufts College Medical School, physician, New England Deaconess Hospital.

§Resident, Medical Out-Patient Department, Children's Hospital.

disease. It possessed an anatomic museum that was amazing in its completeness and in the arrangement of its specimens. Similarly, the Museum of Medical History in the University of Rome was extraordinarily well planned and filled with invaluable medical incunabula and exhibits. Original research on malaria was outstanding. Recent and quite modern buildings were to be seen in many of the medical centers, and in some, equipment of the finest quality and most recent pattern was available. It was evident that high medical standards were more universal and more widespread in Italy than in Greece, probably because of the greater age and number of Italian universities with their cherished traditions of many centuries.

As in Greece, however, there were gaps in medical knowledge, medical equipment and medical procedures. The student overload was just as apparent, in Rome, for example, there were said to be nearly 6000 medical students in the University. With few exceptions similar overcrowding appeared to be the case throughout all the medical schools in Italy. In spite of many individual brilliant clinicians and professors, the teaching load was so great that it was impossible to provide adequate instruction except at a lecture level. Bedside teaching was being carried out but by comparison with American standards was poor as far as quality and quantity were concerned. Laboratory investigations were limited by the variation in equipment and supplies to be found in the different laboratories. As in Greece, it was evident that interest in the fundamental sciences, as far as instruction of medical students goes, left much to be desired. Training in biochemistry lagged far behind, and a real understanding of and interest in physiologic processes was frequently superficial rather than basic and profound. Modern concepts of the treatment of nutritional disturbances, particularly in relation to preoperative and postoperative care, were little understood and would have been difficult to carry out because of actual food shortages. Ancillary services such as social service and occupational therapy were rudimentary, accurate follow-up study of therapeutic measures was difficult and with few exceptions unobtainable.

In Italy, however, possibly because of a more stabilized political and social situation, medical

progress was being made, and a good deal of optimism was evident. Political uncertainties were still apparent, and the threat of great events that might again disturb forward progress in scientific and other realms was apprehended in all conversations. Even more than in Greece, interest and enthusiasm for American methods were evident, this was due at least in part to the fact that many of the ablest Italian physicians and surgeons were personally acquainted with the American trend of thought. In fact, throughout the European phase of the Mission, innumerable friendly contacts that had been interrupted by the war were re-established. As in Greece, the inequalities existing between the inner few and the remainder of the population were noticeable. A desire for American aid was frequently balanced by a lack of desire to depart from the *status quo* of those who were socially and economically in the more fortunate groups. This applied particularly to nonprofessional people encountered outside the medical centers. Almost everywhere an urgent wish was apparent, however, for American aid and co-operation. Again it should be mentioned, as in Greece, that vigorous anti-malaria measures have resulted in almost complete eradication of this disease in the peninsula, at least as compared to its previous prevalence. Preventive medicine and public-health measures as well as nutritional problems were talked about frankly but as yet are but inadequately met, particularly in the southern part of the country. Reconstruction is going on apace, and hope for steady forward progress was everywhere evident.

* * *

In short, the experience of the Mission to Greece and Italy was similar to that of the missions to Czechoslovakia and Austria of 1946 and 1947, in that it was possible to achieve a satisfactory approach to the leaders of the medical profession in a friendly scientific spirit, unbiased by political events or internal difficulties. These difficulties were only too obvious at times, but frank, earnest discussions were possible and mutual contributions were made that were of great value. Probably as important as anything else was the re-establishment of friendly professional relations between groups that had been cut off from normal scientific contacts for many years.

receiving suction ranged from 10 cc to 36 cc with an average of 20 cc. Of the 5 infants delivered by low forceps (Table 5) 1 infant whose gastric contents totaled 14 cc had respiratory difficulty immediately after delivery. The other infants yielded 0 to 7 cc and had a normal course.

Infants of Nondiabetic Mothers

Two of the 12 infants delivered by section (Table 3) developed respiratory difficulty, and the gastric contents in this group averaged 14 cc, with a range of 6 cc to 28 cc. Because of the small numbers of infants it appears futile to compare the incidence of abnormal respiratory signs in infants of diabetic mothers delivered by section with that of infants of nondiabetic mothers similarly de-

TABLE 3 Course in Infants of Nondiabetic Mothers Delivered by Cesarean Section Because of Disproportion in Whom Gastric Suction Was Performed

INFANT No	BIRTH WEIGHT		VOLUME OF GASTRIC CONTENTS	CLINICAL COURSE
	lb	oz	cc	
1	8	2	10	Normal
2	7	1	14	Retraction and cyanosis at birth clearing in fifteen minutes remainder of course normal
3	8	4	28	Normal
4	5	8	10	Normal
5	5	14	19	Retraction at birth, mild cyanosis at twelve hours together with retractions lasted two days.
6	8	11	8	Normal
7	6	10	12	Normal
8	7	7	21	Normal
9	7	1	16	Normal
10	6	15	14	Normal
11	8	4	17	Normal
12	5	10	6	Normal

livered. None of the infants of nondiabetic mothers delivered by low forceps (Table 4) developed abnormal respiratory signs, the average quantity of gastric contents was 2 cc, with a range of 0 cc to 7 cc.

As a result of these preliminary studies the following conclusions seem justified: infants of nondiabetic mothers delivered by low forceps have very small amounts of gastric contents, infants of diabetic and nondiabetic mothers delivered by cesarean section have large amounts of gastric contents immediately after birth, and gastric suction in infants of diabetic mothers delivered by section appears to decrease the frequency of respiratory difficulty following birth.

DISCUSSION

It has been a matter of record for some years that the incidence of respiratory difficulty is higher after cesarean section than after delivery through the pelvis.²⁻⁹ Several factors have been demonstrated to be responsible for the initial apnea seen in infants delivered by section: general anesthetics

and certain analgesics, notably morphine, have been repeatedly shown to produce depression.^{5, 7, 8, 10, 11} Some of the maternal indications for section such as placenta previa and premature separation are in themselves injurious to the infant because of oxygen deficiency in utero. Premature

TABLE 4 Course in Infants of Nondiabetic Mothers Delivered by Low Forceps in Whom Gastric Suction Was Performed

INFANT No	BIRTH WEIGHT		VOLUME OF GASTRIC CONTENTS	CLINICAL COURSE
	lb	oz	cc	
1	5	2	20	Normal
2	7	4	10	Normal
3	7	8	15	Normal
4	6	5	0	Normal
5	9	1	10	Normal
6	8	4	40	Normal
7	7	4	60	Normal
8	7	7	0	Normal
9	6	1	10	Normal
10	5	10	0	Normal
11	8	2	0	Normal
12	8	7	40	Normal
13	6	9	70	Normal
14	5	—	40	Normal
15	4	9	0	Normal

infants, whatever the reason for prematurity, do not stand section well.⁶

Several observers have suggested that physiologic birth through the pelvis has a role in the preparation of the infant for extrauterine respiration. The role is unfilled when birth is by section, and its lack may be productive of delayed respirations. Bloxson^{11, 12} suggests that the intermittent pressure of the uterine contractions upon the chest wall may condition the infant to postnatal respiratory movements, the uterine contractions may indirectly influence the onset of breathing by accustoming the respiratory centers to fluctuating levels of

TABLE 5 Course in Infants of Diabetic Mothers Delivered by Low Forceps in Whom Gastric Suction Was Performed

INFANT No	BIRTH WEIGHT		VOLUME OF GASTRIC CONTENTS	CLINICAL COURSE
	lb	oz	cc	
1	8	7½	7	Normal
2	4	4	14	Weak cry at birth, rapid respirations and retraction lasting ten hours.
3	6	15	2	Normal
4	7	8	4	Normal
5	7	7	0	Normal

oxygen and carbon dioxide produced by the fluctuating placental blood flow. Moulding of the head as it passes through the birth canal produces a local excess of carbon dioxide in the head, and it is this excess of oxygen in the medulla, and through respiration, certainly, intrauterine inductive of respiratory motions in the infant.

It has been suggested that the pelvis performs a physiologic cl

procedure was repeated by the nurse on duty every three hours for twelve hours. No attempt to reduce oxygen was made until the fourth day of life. Glucose feedings were started at thirty-six to forty-eight hours after birth, and a 2 per cent milk formula at seventy-two hours. All infants received their feedings in the incubator and were under constant observation by nurses with long experience in the care of infants of diabetic mothers. Daily physical examinations were performed by the same physician. Examination of the gastric

marized in Table 4. Finally, 5 infants of diabetic mothers delivered by low forceps, whose gastric contents were measured, are included in Table 5. Figures for gastric contents apply only to the material obtained within the first few minutes after delivery. Material obtained subsequently was not included.

RESULTS

Infants of Diabetic Mothers

The small number of patients studied, together with variables introduced by differences in birth

TABLE 2 *Course of Infants of Diabetic Mothers Delivered by Cesarean Section in Whom No Gastric Suction Was Performed*

INFANT No	BIRTH WEIGHT		CLINICAL COURSE
	lb	oz.	
1	6	15	Normal
2	8	4	Infant normal at birth, on second day began to retract and respirations became rapid, was normal by third day
3	8	1	Infant normal at birth on second and third days retracted considerably and was moderately cyanotic, and respiratory rate was increased course normal thereafter
4	5	5	Cyanosis and retraction at birth on second day retractions continued but color was good on third day retractions ceased on seventh day patient became cyanotic cyanosis cleared with oxygen and course subsequently normal
5	8	4	Normal
6	5	8	Normal
7	5	3	Infant normal at birth but suddenly developed retractions and increased respiratory rate at two hours on second day had three cyanotic attacks together with persisting retractions and elevated respiratory rate, course subsequently normal
8	9	8	Slowly clearing cyanosis at birth retraction and increased respiratory rate which continued through first five days, on third day respirations became very labored after fifth day course normal
9	6	6	Normal
10	6	4	Infant normal at birth, on second day became cyanotic, and had cyanotic attacks during first ten days, thereafter course normal
11	8	4	Infant normal at birth on second day developed cyanosis and retractions which were intermittent for two days and then disappeared
12	5	9	Infant normal at birth, on sixth day developed cyanosis while oxygen was not being administered but cyanosis cleared with oxygen and course normal thereafter
13	4	1	Cyanosis and retraction at birth cyanosis cleared, but infant continued to retract for three days.
14	10	—	Moderate cyanosis and retraction at birth, cyanosis cleared in oxygen but retractions continued for two days.
15	7	14	Infant normal at birth On second third and fourth days moderate retraction
16	7	5½	Normal
17	7	8½	Normal
18	6	9½	Cyanosis at birth with increased respiratory rate retractions and complaining cry on second day color improved and complaining cry was gone patient continued to have intermittent cyanosis during first seven days
19	7	1	Normal
20	6	4	Infant normal at birth moderate cyanosis and retractions began at six hours and lasted approximately fourteen hours
21	8	14	Normal
22	9	3	Infant normal at birth three hours later developed sudden increase in respiratory rate with cyanosis and retractions lasting twenty four hours
23	8	2	Normal
24	8	6	Normal
25	10	2	Retraction and cyanosis at birth these signs cleared in subsequent three hours but increased respiratory rate persisted for two days

contents revealed the presence of cornified epithelial cells, lanugo hair and shreds of blood and mucus.

In Table 1 are listed the birth weights of the infants, the total quantity of gastric contents and the positive findings, if any, noted during the early neonatal period. In Table 2 similar data for the control group of infants in whom gastric suction was not performed are recorded. Identical studies were conducted on infants of nondiabetic mothers delivered at term under spinal anesthesia by cesarean section because of disproportion. These infants were delivered by various obstetricians, the findings are summarized in Table 3. To compare the quantities of gastric contents of such infants with those of infants delivered by low forceps, an additional group was studied and is sum-

marized in Table 4. Finally, 5 infants of diabetic mothers delivered by low forceps, whose gastric contents were measured, are included in Table 5. Figures for gastric contents apply only to the material obtained within the first few minutes after delivery. Material obtained subsequently was not included.

The small number of patients studied, together with variables introduced by differences in birth weight, severity and duration of diabetes in the mother, ease and rapidity of delivery and so forth, makes a statistical comparison of the "diabetic" groups impossible. However, the clinical course of the two groups of infants differs considerably. Four infants in the group receiving gastric suction (Table 1) developed mild respiratory difficulties, in all 4, abnormal respiratory signs were present at birth. Of the 25 infants who did not receive suction (Table 2) 15 developed respiratory difficulties, 9 of these were normal at birth, and respiratory embarrassment subsequently appeared. The severity of respiratory embarrassment was much more marked in this group of infants. There were no deaths in either group, and all infants breathed spontaneously at birth. The gastric contents obtained in the group

respiratory difficulty. Of 25 infants in whom suction was not performed 15 developed respiratory difficulty, in 6 it was present at birth, but 9 of the fifteen showed a delayed onset of obstructive signs.

The average quantity of gastric contents in infants of diabetic mothers, all of whom were delivered by cesarean section was 20 cc. An average of 14 cc of fluid was obtained from the stomachs of infants of nondiabetic mothers delivered by cesarean section because of disproportion. Infants of nondiabetic mothers delivered by low forceps yielded an average of 2 cc.

In view of the marked difference in the neonatal course of infants who received gastric suction and of those who did not, it is proposed that gastric suction at birth be carried out in infants delivered by cesarean section, in addition to the procedures now commonly employed for the prevention of asphyxia. Whether or not gastric suction will affect the clinical course of infants of nondiabetic mothers delivered by cesarean section remains to be determined.

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GYNECOMASTIA IN ASSOCIATION WITH CHRONIC ULCERATIVE COLITIS*

LAURENCE H. KYLE, M.D.†

WASHINGTON, D. C.

DURING recent months the problem of gynecomastia has received increasing attention, especially its association with impaired hepatic function^{1,2} and malnutrition.³⁻⁵ Among the complications of chronic ulcerative colitis, liver disease has most recently attracted attention.⁶⁻⁸ The following case report is that of a patient with chronic ulcerative colitis who showed both hepatic impairment and gynecomastia and whose clinical picture was of such a nature as to allow some speculation regarding the pathogenesis of the latter condition.

CASE REPORT

A 24-year-old man had been in excellent health until 1944. At that time he developed frequent, painful, urgent, bloody, often watery stools, together with loss of appetite, weight and strength. Examination in an Army general hospital revealed no significant abnormalities. After a period of intensive therapy with antibiotics, a high-vitamin diet

parenteral administration of liver and a number of anti-diarrhea compounds improvement took place, and the patient was discharged with a diagnosis of simple diarrhea. He remained well for about 6 months until, in April, 1945, the symptoms recurred. Further studies were performed, and a diagnosis of chronic ulcerative colitis was made after sigmoidoscopic examination. Mild symptoms continued throughout 1945. During the first 2 or 3 months of 1946 the patient was asymptomatic, but in April the original symptoms returned with full severity and continued throughout the summer with some amelioration in the early fall.

During November and December, 1946, together with recrudescence of marked gastrointestinal symptoms, there was a severe attack of polyarthritides. Throughout the early part of 1947 he continued to have severe diarrhea, and there was a steady loss of weight. In March glycosuria and hyperglycemia were first noted, small doses of insulin were given and after a time the glycosuria disappeared. The patient had never shown glycosuria previously, and the family history was entirely negative for diabetes.

In May, 1947, the intestinal symptoms had become so severe and loss of weight so profound, that ileostomy was performed. After this procedure there was marked improvement, with a return of appetite and a steady gain of weight.

The patient continued a very high vitamin B intake for some weeks after the operation, but then, since he felt so well, he began to discontinue the use of extra vitamins until finally, in the latter part of the summer, he was taking no supplementary vitamins of any sort. Glycosuria reappeared, and large doses of insulin were necessary for control. Shortly

*From the Medical Service, Georgetown University Hospital, and the Department of Medicine, Georgetown University School of Medicine.

†He was reported in this paper was completed during the tenure of a research fellowship in endocrinology at the National Cancer Institute.

†Instructor in medicine and William Wade Hinchey Cancer Research Fellow, Department of Medicine, Georgetown University School of Medicine. Visiting physician, Georgetown University Hospital.

respiratory tract by the compressive action of the birth canal upon the chest of the infant¹⁴⁻¹⁷ and that such cleansing serves to remove much debris that would otherwise be aspirated with the first breath. Russ and Strong^{9, 18} have demonstrated this by their findings of increased amounts of material in the tracheas of infants delivered by cesarean section. The improvement in mortality rate and in the incidence of respiratory difficulty that they found after the use of routine tracheal catheterization attests to the practicality of their observations.

In infants delivered by cesarean section a syndrome of delayed respiratory difficulty of an obstructive nature has been repeatedly described with unusual uniformity^{9, 17, 18} a presumably normal infant, after cesarean section and routine newborn care, develops signs of respiratory distress minutes to hours after delivery. There may be mild or marked inspiratory retraction, with dyspnea, tachypnea and cyanosis. Restlessness, a weak, high-pitched cry and at times convulsions may be present. Oxygen therapy is efficacious at the start, but the signs tend to recur with increasing severity and decreasing response to oxygen, death may ultimately occur with cyanosis and respiratory obstruction.

The cause of this delayed respiratory distress may logically be sought in the process of birth itself. The observations of Russ and Strong^{9, 18} provide one explanation. The increased amount of fluid in the upper respiratory tract of these infants must necessarily be inhaled with the first breath unless removed by the physician. That this may not produce immediate symptoms is shown by the autopsy findings of Russ and Strong and by the observations of Farber and Sweet¹⁹. Aspirated material at first lies loosely distributed in the alveolar spaces, but each successive breath packs the debris against the alveolar walls, forming the "asphyxial membrane" composed of amniotic detritus, meconium, lanugo and vernix. Delayed respiratory obstruction is dependent on an increasingly impervious intra-alveolar membrane.

Potter and Rosenbaum¹⁷ have described an increase in the amount of cerebrospinal fluid producing external hydrocephalus at autopsy in this syndrome. Since asphyxia causes a transudate as an early manifestation²⁰ they believe that asphyxia is responsible for this syndrome, perhaps supported by the effect of the sudden pressure changes incident to abdominal delivery.

The present paper attempts to add another possible cause of delayed respiratory distress of the infant delivered by cesarean section—namely, ingestion with subsequent regurgitation and aspiration of amniotic fluid, blood and mucus. It is further suggested that routine gastric suction immediately after delivery by section should be performed in addition to the accepted measures

for neonatal care. Mention of the use of gastric suction is not made in any of the standard textbooks of obstetrics or pediatrics. A review of the literature over the past thirty years, however, reveals that Slawik,²¹ in 1925, recommended gastric lavage within the first two hours of life whenever asphyxia was present or the amniotic fluid appeared contaminated. He proposed thereby to prevent absorption of bacteria through the gastrointestinal mucosa, with consequent generalized sepsis, and to prevent aspiration of the material into the lungs. Although he reported that gastric suction was without harmful effects, he failed to advance convincing evidence of the validity of his proposal. The literature presents few figures on gastric contents of normal newborn infants with which to compare our findings. Only fifteen observations are recorded within one hour of birth^{22, 23}, the average content is 4.9 cc, with a range of 0.5 to 10.0 cc. If observations in the first twenty-four hours of life are included, 119 cases are available^{22, 24}, here the range is 0.5 to 12 cc, with an average of 3.7 cc. The average anatomic capacity of the newborn stomach is given as approximately 30 to 35 cc²⁵⁻²⁷. Although our series is small, it is evident that the gastric content of infants delivered by cesarean section is greater than that of infants delivered through the pelvis and, in some cases, approaches the maximum distensibility or anatomic capacity of the stomach. Whether or not the greater volume of gastric contents in infants of diabetic mothers is related to hydramnios, which occurs frequently in the pregnant diabetic patient, remains to be investigated.

To determine the value of gastric suction in the neonatal care of infants delivered by cesarean section a much larger group of normal infants together with controls will be required, the present study is subject to criticism because of the large number of infants of diabetic mothers.

SUMMARY

In an unpublished review of the neonatal course of the infants of diabetic mothers the outstanding abnormal signs consisted of cyanosis, dyspnea, tachypnea and retraction of the soft parts of the chest. These signs occurred immediately at birth or within several hours of birth. The majority of the infants were delivered by cesarean section, such signs not infrequently complicate the course of infants of nondiabetic mothers delivered by section. On the supposition that delayed respiratory signs of an obstructive nature might be due to the ingestion of large amounts of amniotic fluid followed by regurgitation and aspiration, a study was conducted on infants of diabetic mothers delivered by section to determine the effect of gastric suction on the frequency of these signs.

Of 25 infants receiving gastric suction at birth, 4 showed respiratory embarrassment that was present at birth, and none developed delayed

gynecomastia has never been definitely established. It is a basic premise that administration of estrogens will cause development of the male breast. In addition, there is considerable laboratory and clinical evidence that estrogens are not normally inactivated when hepatic function is impaired. Consequently, one feels quite secure in holding to the theory that gynecomastia in liver disease results from an excessive amount of circulating estrogen. Other features of cirrhosis attributable to an excessive amount of circulating estrogen are spider angiomas, testicular atrophy, "liver palms," decreased growth of axillary hair, impotence and

151 patients with colitis and noted in all marked hypoalbuminemia that was strikingly refractory to treatment. Johnson⁷ reviewed 25 cases of chronic ulcerative colitis and found that a palpable liver had been noted in 5. Two of these patients were studied and proved to have hepatic insufficiency. After reviewing the possible causes of the insufficiency he concluded that a combination of the factors of poor nutrition and absorption of toxic substances from a diseased bowel could be operative.

During World War II the incarceration of large numbers of prisoners by the Japanese provided an optimal environment for the development of malnutrition on a mass scale. In addition to other developments in prisoners kept for long periods on semi-starvation diets, gynecomastia was frequently noted. Malnutrition in its far-reaching effects on the human organism provides a number of possible mechanisms for the development of gynecomastia.

TABLE 1 Major Causes of Gynecomastia

Testicular tumors
Teratomas and choriocarcinomas
Interstitial-cell tumors (? adrenal-cell rests)
Testicular atrophy
Klinefelter's syndrome
Secondary to cirrhosis, trauma and so forth
Hepatic cirrhosis
Infectious hepatitis
Malnutrition
Hyperthyroidism
Adrenal disease
Cortical tumors or hyperplasia
Addison's disease
Therapy with desoxycorticosterone acetate or cortical extract
Treatment with estrogenic hormones
Treatment with androgenic hormones
Miscellaneous
Prostatectomy
Pulmonary disease
Leprosy and so forth

loss of libido in the male, and change of menstrual pattern in the female. The possibility that testicular atrophy in patients suffering from cirrhosis of the liver develops on a nutritional basis and the well documented association of other types of testicular atrophy with gynecomastia lend some support to the idea that gynecomastia in liver disease may be secondary to testicular changes. However, experimental production of testicular atrophy by administration of estrogens, especially in the presence of hepatic disease, validates the concept that both this complication and that of mammary enlargement may be due to insufficient inactivation of estrogens.¹⁰ The liver disease usually accompanied by gynecomastia is cirrhosis. Edmondson¹¹ noted this fact and asked why a similar development could not take place in less chronic liver disease. Since then Klatskin² has reported 2 cases of gynecomastia in patients with infectious hepatitis.

It is of interest that the patient described above showed histologic evidence of hepatic disease. Considerable attention has recently been paid to the frequency of hepatic disease in patients suffering from chronic ulcerative colitis. Tumen, Monaghan and Jobb⁶ reported 5 cases with cirrhosis among

Undernourishment may cause hypofunction of the pituitary body, with consequent secondary impairment of activity of such target endocrine organs as the adrenal glands and gonads.

Testicular atrophy may result from deficiencies of specific nutrients necessary for preservation of testicular structure and function.

Vitamin deficiency, especially lack of components of the B complex, could well be the important factor. Of interest in this regard is the experimental work of Biskind,¹²⁻¹³ who found that whereas inactivation of estrogen requires the presence of adequate amounts of vitamin B, androgen inactivation does not. Consequently changes in the androgen-estrogen ratio could readily occur in patients deprived of these vitamins.

Hepatic impairment of a primary type or aggravation of latent mild liver disease with consequent inactivation of estrogens as outlined above must be considered as a possibility in all poorly nourished patients.

One of the most interesting features of the gynecomastia seen in malnourished prisoners of war was either primary development or increase in severity when the prisoners were allowed a more liberal diet. This observation, made first by Klatskin² and later elaborated upon by Jacobs,³ may have considerable bearing on the pathogenesis of certain types of gynecomastia and is directly applicable to the case reported above. Jacobs has suggested that during the period of starvation lack of normal amounts of hormone-building material results in deficient production of the steroid hormones. This deficiency is rapidly overcome upon resumption of a more adequate diet. The hepatic impairment resulting from prolonged malnutrition is slower of recovery, with consequent temporary lack of inactivation of the newly formed estrogens.

thereafter the patient first noticed a tender mass in the left breast. This mass increased in size, and soon thereafter a similar mass appeared in the other breast. At about the time that the breast changes were most severe, the patient underwent colectomy. At this time both breasts showed firm, well demarcated masses measuring in diameter 5 cm on the right and 3.5 cm on the left. They were freely movable, and the one on the right was tender. There was a moderate amount of palmar erythema, but no cutaneous telangiectasias were observed. Both testes were present in the scrotum and were of normal size and consistence. The patient could recall no previous occurrence of mammary tenderness or enlargement.

Liver biopsy taken at the time of the colectomy showed early parenchymatous degeneration, with slight fibrosis. The postoperative course was very stormy. The diabetes increased greatly in severity, and the patient became mildly jaundiced. However, during the next few weeks there was gradual improvement on a therapeutic regimen that included high-vitamin intake, blood transfusions, antibiotics and insulin. At this time the gynecomastia gradually diminished. Shortly after discharge from the hospital he continued to improve, and the glycosuria subsided to a point where only

ulcerative colitis could well have been associated with impaired hepatic function. Of further interest is the fact that there was marked increase in the severity of the diabetes during the period when the gynecomastia appeared. Some correlation may be seen between the increase in severity of the diabetes and the cessation of adequate intake of vitamin B. However, the increased insulin requirement can also be correlated with increased caloric intake.

Although breast enlargement in the male is occasionally due to a neoplasm, by far the more common causes are either excessive deposition of fat (pseudogynecomastia) or development of glandular tissue similar to that of the female breast (true gynecomastia). These conditions are frequently confused. Gynecomastia may be divided into three

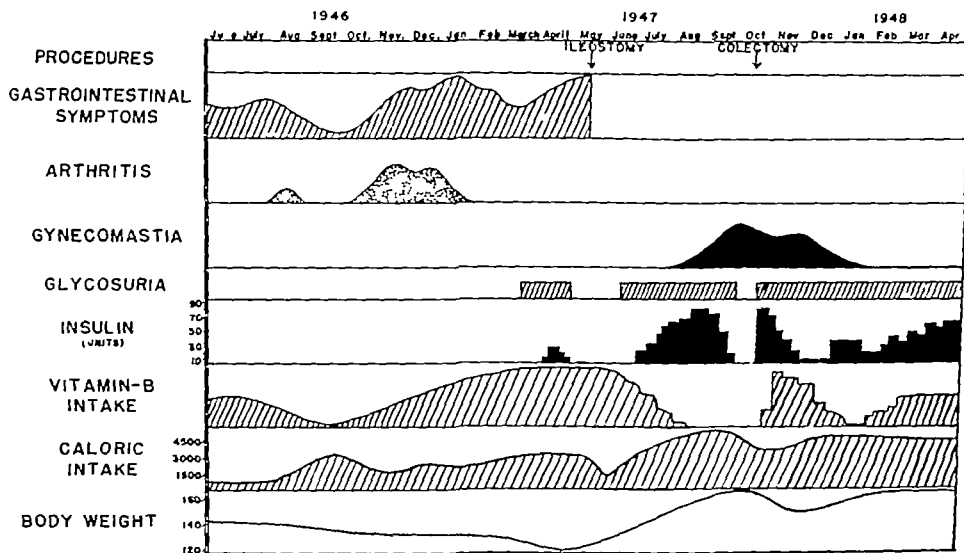


FIGURE 1 Clinical Course

small doses of insulin were required. At this time a decrease of the vitamin intake was again followed by aggravation of the diabetes but without any further changes in the breasts, which then showed barely palpable masses. Again, after a more adequate intake of vitamins, there was improvement of the diabetes. This improvement, however, was only temporary, and since that time the patient has continued to require large doses of insulin even though on a very adequate vitamin intake. The salient features of the clinical course are shown in Figure 1.

DISCUSSION

Several points are worthy of emphasis. Although there was evidence of hepatic disease the gynecomastia did not develop while the liver disease was presumably most severe. Rather, the mammary enlargement appeared when the patient was eating heavily, gaining weight and in much improved general condition, but at a time when he was beginning to neglect his vitamin intake.

The development of diabetes without the usual familial background and during the height of the

forms that appearing in boys at the time of puberty, referred to by Jung⁹ as the subareolar node, idiopathic or "nonhormonal," a type described much more frequently in the surgical than in the medical literature and less often described since the advent of more intensive metabolic studies, and true or "hormonal" gynecomastia. The last type is seen in numerous conditions, the majority of which allow a fairly reasonable hypothesis regarding the pathogenesis of the mammary enlargement. The more important causes of true gynecomastia are summarized in Table 1. Only those types that have a possible application to the case reported here are discussed in any detail.

Gynecomastia has been noted for many years as a not uncommon feature of hepatic cirrhosis. When testicular atrophy is also present, the combination is referred to as the Silvestrini-Corda syndrome. The mechanism of the development of

gynecomastia has never been definitely established. It is a basic premise that administration of estrogens will cause development of the male breast. In addition, there is considerable laboratory and clinical evidence that estrogens are not normally inactivated when hepatic function is impaired. Consequently, one feels quite secure in holding to the theory that gynecomastia in liver disease results from an excessive amount of circulating estrogen. Other features of cirrhosis attributable to an excessive amount of circulating estrogen are spider angiomas, testicular atrophy, "liver palms," decreased growth of axillary hair, impotence and

151 patients with colitis and noted in all marked hypoalbuminemia that was strikingly refractory to treatment. Johnson⁷ reviewed 25 cases of chronic ulcerative colitis and found that a palpable liver had been noted in 5. Two of these patients were studied and proved to have hepatic insufficiency. After reviewing the possible causes of the insufficiency he concluded that a combination of the factors of poor nutrition and absorption of toxic substances from a diseased bowel could be operative.

During World War II the incarceration of large numbers of prisoners by the Japanese provided an optimal environment for the development of malnutrition on a mass scale. In addition to other developments in prisoners kept for long periods on semi-starvation diets, gynecomastia was frequently noted. Malnutrition in its far-reaching effects on the human organism provides a number of possible mechanisms for the development of gynecomastia.

TABLE 1 Major Causes of Gynecomastia

Testicular tumors
Teratomas and choriocarcinomas
Interstitial-cell tumors (? adrenal-cell rests)
Testicular atrophy
Klinefelter's syndrome
Secondary to orchitis, trauma and so forth
Hepatic cirrhosis
Infectious hepatitis
Malnutrition
Hyperthyroidism
Adrenal disease
Cortical tumors or hyperplasia
Addison's disease
Therapy with desoxycorticosterone acetate or cortical extract
Treatment with estrogenic hormones
Treatment with androgenic hormones
Miscellaneous
Prostatectomy
Pulmonary disease
Leprosy and so forth

loss of libido in the male, and change of menstrual pattern in the female. The possibility that testicular atrophy in patients suffering from cirrhosis of the liver develops on a nutritional basis and the well documented association of other types of testicular atrophy with gynecomastia lend some support to the idea that gynecomastia in liver disease may be secondary to testicular changes. However, experimental production of testicular atrophy by administration of estrogens, especially in the presence of hepatic disease, validates the concept that both this complication and that of mammary enlargement may be due to insufficient inactivation of estrogens.¹⁰ The liver disease usually accompanied by gynecomastia is cirrhosis. Edmondson¹¹ noted this fact and asked why a similar development could not take place in less chronic liver disease. Since then Klatzkin² has reported 2 cases of gynecomastia in patients with infectious hepatitis.

It is of interest that the patient described above showed histologic evidence of hepatic disease. Considerable attention has recently been paid to the frequency of hepatic disease in patients suffering from chronic ulcerative colitis. Tumen, Monaghan and Jobb⁶ reported 5 cases with cirrhosis among

Undernourishment may cause hypofunction of the pituitary body, with consequent secondary impairment of activity of such target endocrine organs as the adrenal glands and gonads.

Testicular atrophy may result from deficiencies of specific nutrients necessary for preservation of testicular structure and function.

Vitamin deficiency, especially lack of components of the B complex, could well be the important factor. Of interest in this regard is the experimental work of Biskind,^{12, 13} who found that whereas inactivation of estrogen requires the presence of adequate amounts of vitamin B, androgen inactivation does not. Consequently changes in the androgen-estrogen ratio could readily occur in patients deprived of these vitamins.

Hepatic impairment of a primary type or aggravation of latent mild liver disease with consequent inactivation of estrogens as outlined above must be considered as a possibility in all poorly nourished patients.

One of the most interesting features of the gynecomastia seen in malnourished prisoners of war was either primary development or increase in severity when the prisoners were allowed a more liberal diet. This observation, made first by Klatzkin² and later elaborated upon by Jacobs,⁵ may have considerable bearing on the pathogenesis of certain types of gynecomastia and is directly applicable to the case reported above. Jacobs has suggested that during the period of starvation lack of normal amounts of hormone-building material results in deficient production of the steroid hormones. This deficiency is rapidly overcome upon resumption of a more adequate diet. The hepatic impairment resulting from prolonged malnutrition is slower of recovery, with consequent temporary lack of inactivation of the newly formed estrogens.

Resumption of adequate caloric intake after a prolonged period of starvation causes rapid depletion of vitamin stores and calls for a greatly increased vitamin intake. As Klatskin² has pointed out, unless the vitamins are supplied a period of relative vitamin deficiency may exist. Inasmuch as estrogen inactivation seems to depend on adequate amounts of vitamin B, whereas that of androgen does not, temporary reversal of the androgen-estrogen ratio may result. When one passes from a state of semistarvation to one of more adequate nutrition the obvious result should be an increase in tissue-affecting hormones secondary to increased pituitary activity or to a more adequate intake of hormone precursors. The theoretical possibility exists that

a number of patients similar to those of Klinefelter so far as tubular destruction was concerned except that Sertoli cells were present. These patients had no gynecomastia, and pituitary gonadotropins were present in normal amounts. McCullagh's¹⁷ report of development of gynecomastia in patients with hypogonadism treated with methyl testosterone lends further support to the probability that the male hormone is potentially able to cause glandular development in the male breast.

Even more confusing is the occurrence of gynecomastia following administration of desoxycorticosterone,^{18, 19} a synthetic steroid hormone that is a potent regulator of salt and water although it cannot ordinarily be implicated as affecting sexual structures. It is not inconceivable that some metabolic product common to several of the steroid hormones is the active mammogenic agent. A diagram expressing the possible mechanism of development of gynecomastia under conditions of hepatic insufficiency, vitamin deficiency and malnutrition is shown in Figure 2.

Why one person develops gynecomastia while another with an identical clinical pattern of disease shows no mammary-gland changes remains a problem. End-organ sensitivity or unresponsiveness can always be advanced as a simple but logical explanation. In this regard the observation of Jacobs⁵ is of interest. He noted that 15 per cent of patients with gynecomastia gave a history of having had previous breast enlargement at the time of puberty. It is possible that the breast in certain male patients is oversensitive and therefore responsive to amounts of circulating estrogen that in other persons are incapable of causing mammary stimulation.

Granting the fact that the pathogenesis of gynecomastia is complex, it remains a clinical entity of considerable diagnostic and therapeutic import. Its appearance should call for investigation aimed in the direction of ruling out all the possible etiologic factors presented in Table 1. When seen in any patient with hepatic disease or with a basic disease that may lead to malnutrition, gynecomastia should be accepted as an indication for more active therapy.

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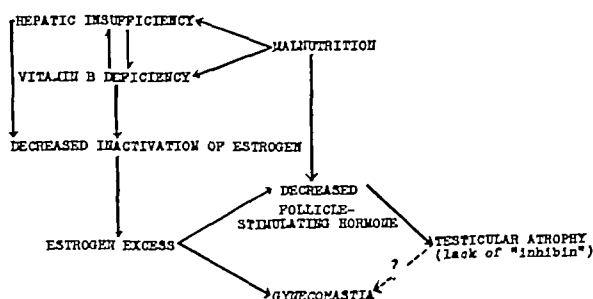


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WHITE RIVER JUNCTION, VERMONT, AND HANOVER, NEW HAMPSHIRE

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CASE REPORT

A 46-year-old laborer entered the hospital on November 14, 1939, for the repair of a left indirect inguinal hernia. A routine roentgenogram of the chest revealed an area of decreased density posteriorly in the medullary portion of the left tenth rib. The area was sharply defined and non-invasive in character, and associated with slight expansion and thinning of the cortex. A radiologic diagnosis of bone cyst was made (Fig. 1).

Examination of the blood disclosed a red-cell count of 4,690,000, with a hemoglobin of 90 per cent, and a white-cell count of 7250, with 64 per cent neutrophils, 34 per cent lymphocytes and 2 per cent monocytes. There were no symptoms or physical findings associated with this lesion. After a left inguinal herniorrhaphy and an uneventful post-operative course the patient was discharged.

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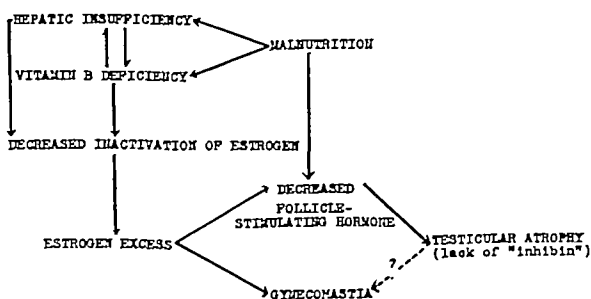


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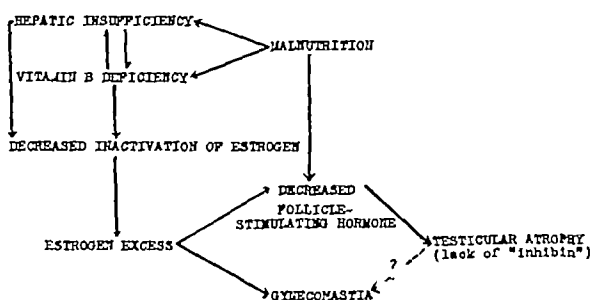


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It is of significant pathological interest that this eosinophilic granuloma was under roentgenologic observation over a period of nine years with no apparent change in size, shape or invasiveness. Yet Lichtenstein and Jaffe⁴ and Green and Farber¹ have observed that these destructive lesions develop rapidly, with tendencies toward bone destruction and spontaneous fractures. Throughout the period of observation, radiologic examination had revealed a circumscribed process, and at operation there was no gross evidence of extension to the periosteum. In confirmation, pathological study also disclosed that the local lesion was totally confined within a capsule of dense cortical bone.

SUMMARY

A case of eosinophilic granuloma of the rib is reported that presented two singular features: the

age of the patient, fifty-five years, when the lesion was diagnosed, and the nine-year period of observation without apparent physical change in the process.

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MEDICAL PROGRESS

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R. H. SMITHWICK, M.D.*

BOSTON

REPORTS dealing with various aspects of surgery of the autonomic nervous system are becoming more numerous each year. It is impossible to comment upon all of them. Consequently certain articles are referred to that have a bearing upon the topics selected for discussion in this review.

ANATOMY

For some time, particularly since Richter¹ devised a practical apparatus for studying the electrical resistance of the skin, surgeons have noted that after the removal of portions of the sympathetic chain and ganglions having to do with the sympathetic innervation of a particular area, evidence of residual pathways to that area still existed. This is particularly true of the anterior half of the thigh from the groin to the knee. In a recent discussion of this matter, Rav and Console² have pointed out that, even after bilateral excision of the sympathetic trunks from the inferior cervical to the fifth lumbar ganglions, residual sympathetic pathways, as judged by low skin-resistance levels, were present from the twelfth thoracic to the third lumbar dermatomes. They found that these pathways could be interrupted by spinal anesthesia, resection of

anterior roots, procaine block or division of the peripheral nerves, or by the administration of tetraethyl ammonium chloride. For some time, Cone³ has been resecting the anterior roots of the twelfth dorsal and first and second lumbar segments to denervate the thigh completely in his modification of thoracolumbar sympathectomy for hypertension. These observations are of interest because they indicate that sympathetic fibers can reach the sweat glands and, by inference, blood vessels, without passing through the paravertebral ganglionated sympathetic chains. It is difficult to believe that these fibers run without a synapse somewhere between the lateral horn and the end organ. The fact that these sympathetic impulses can be interrupted by tetraethyl ammonium chloride, which blocks transmission at the synapses in sympathetic ganglions, suggests that ganglionic tissue exists. It is apparent, however, that it is somewhere other than in the usual thoracic and lumbar ganglions. A possible explanation is contained in a recent article by Skoog,⁴ who found sympathetic ganglions in the communicating rami between the cervical and upper two thoracic ganglions and the spinal nerves. There was no regularity about their location. At times they were situated not far from the ganglionated chain, but at times they were very

*Professor of surgery, Boston University School of Medicine; surgeon-in-chief, Massachusetts Memorial Hospitals.

blood demonstrated a red-cell count of 4,240,000, with a hemoglobin of 13.6 gm, and a white-cell count of 7200, with 60 per cent neutrophils, 31 per cent lymphocytes, 6 per cent monocytes and 3 per cent eosinophils, the sedimentation rate was 23 mm in 1 hour.

On June 12, under a local field block of 1 per cent novocain, a subperiosteal partial resection of the left tenth rib was carried

At follow-up examination 6 months later, there was no pain in the left side of the chest. Physical examination disclosed a healed operative incision posteriorly over the course of the left tenth rib. Complete roentgenologic examination of the skeleton demonstrated no local recurrence of the original lesion but disclosed discrete areas of decreased density, consistent with the early bony lesions of eosinophilic granuloma, in the left parietal bone and in the spine of the first cervical vertebra. The patient was discharged to return in 3 months for further evaluation.

DISCUSSION

Analysis of approximately 46 cases reported to date in the literature has shown an age incidence ranging from eleven months¹ to thirty-nine years,² with the preponderance of cases in young children.



FIGURE 2 X-ray Film Taken on February 26, 1948, Showing the Same Cystic Lesion of the Left Tenth Rib

out. The lesion was a symmetrical, circumscribed mass without gross evidence of extension into the surrounding tissue.

The pathological report (S-48-120) was as follows:

The specimen consists of a 6.5-cm segment of rib. In the midportion there is a fusiform swelling measuring 2.5 by 2 by 1 cm. The external surface is smooth, firm and mottled gray yellow. Section through this enlargement exhibits soft yellow-pink and brown tissue bordered by gray tissue of increased consistence. The entire lesion is surrounded by a layer of cortical bone, 2 to 3 mm in thickness.

On microscopical examination of all tissue blocks fixed in 10 per cent formalin, decalcified in 5 per cent nitric acid and stained with hematoxylin and eosin, the major part of each section consists of a vascular connective tissue containing solid sheets of macrophages with light-staining oval or lobulated nuclei and abundant cytoplasm. The cytoplasm exhibits abundant minute vacuoles. In a few areas there are focal accumulations of histiocytes and eosinophils. Encapsulating this lesion is a relatively avascular narrow border of connective tissue containing bone spicules adjacent to normal cortical bone (Fig. 3). The pathological diagnosis is eosinophilic granuloma.

Convalescence was uneventful, and the patient was discharged from the hospital 5 days after operation.

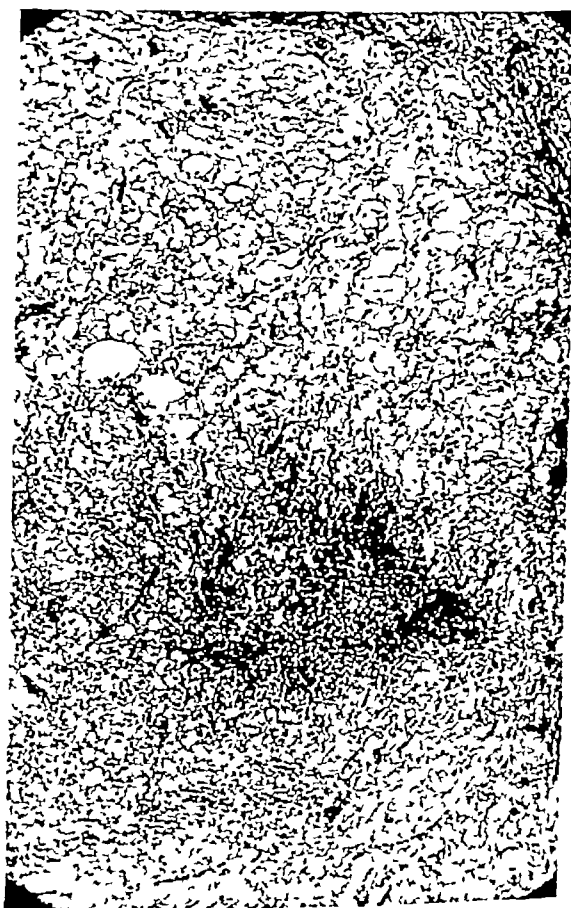


FIGURE 3 Central Portion of the Lesion
Note the abundant foamy-type macrophages with one focal accumulation of histiocytes and eosinophils (hematoxylin and eosin stain $\times 32$)

In 1944, Versiani et al.³ presented a case report of a fifty-year-old woman with an eosinophilic and xanthomatous granuloma of the femur associated with diabetes insipidus, which was finally classified as a variation of Hand-Schüller-Christian disease. Thus, our patient, who was forty-six years of age when the lesion was first noted and fifty-five years

urecholine Doryl appears to be less effective and is more toxic

After resection of the vagus nerves, the fasting free acid levels are decreased by a third or more, and the secretory responses to sham feeding and insulin hypoglycemia are abolished. Evidence concerning the effect of operation upon the chemical or gastric phase of gastric secretion is conflicting. Stein and Meyer²⁰ report a marked reduction in the secretory response to histamine, whereas Schoen and Griswold²¹ find no significant change and believe that the histamine effect is independent of the vagus innervation. Different methods for studying gastric secretion were used by these two sets of authors, the former employing continuous suction and the latter intermittent aspiration with phenol red as an indicator to enable them to estimate emptying and secretory rates. They believed that this technique was more accurate than continuous suction, and the differences observed might possibly be explained on this basis. On the other hand, most observers use continuous suction, and the majority have noted a material reduction in the secretory response to histamine after resection of the vagus nerves. If this is so, it suggests that the presence of acetylcholine, the chemical mediator of parasympathetic impulses, potentiates the action of histamine. Stein and Meyer refer to evidence reported by Necheles et al.²² and by Gray and Ivy²³ indicating that this is the case. It therefore would not be surprising if after resection of the vagus nerves the secretory response to histamine was decreased. It is apparent from the observations of Wangenstein et al.²⁴ that epinephrine potentiates the action of histamine. There is evidence also that in low concentration, epinephrine potentiates the action of acetylcholine.²⁵ In other words, it is conceivable that the antral factor in man, presumably a histamine-like substance if not histamine, the vagal factor, presumably acetylcholine, and the sympathetic factor, presumably an epinephrine-like or sympathin-like substance, not only play independent roles in gastric secretory mechanisms but also may potentiate one another.

Naide and Sayen²⁶ have described a method of study that enables them to place patients with peripheral vascular disease into one of two groups on the basis of basal vascular tone. A person is regarded as having high vascular tone if the tips of the digits of the hands cool to below 25°C after fifteen minutes' exposure to a constant room temperature of 20°C, unclothed except for a light gown. If the digits do not cool to this level the subjects are regarded as having low vascular tone. The authors believe that patients in the latter group will develop adequate collateral circulation in the presence of obliterative vascular disease of the lower extremities, whereas those who have high vascular tone will not. It is their practice to recommend sympathectomy for patients with high vascular tone and

conservative treatment for those with low vascular tone and obliterative vascular disease. The principle of this method of study is logical and is one that I have used for many years.⁹ By study of the vascular responses of a patient to a cool environment it is possible to divide persons into various categories according to the activity of their vasoconstrictor mechanism. In deciding whether sympathectomy will improve the peripheral circulation in a given case, what one really wishes to know is to what extent vasoconstriction of sympathetic origin is capable of reducing the peripheral blood flow. In discussing his experiences with the basal vascular tone test of Naide and Sayen,²⁶ Rector²⁷ pointed out that the various tests in common use today depend upon the demonstration of an increase in circulation after blocking of the sympathetic supply to an extremity. These do not measure the degree of vasoconstriction primarily but indicate whether the denervated vascular bed is capable of maximal vasodilatation. The fact is that there are patients whose peripheral circulation can be greatly reduced by vasoconstriction but cannot dilate maximally in the absence of neurogenic vasoconstriction. They can be helped by sympathectomy but might not be regarded as suitable for this operation on the basis of usual tests. Some method of study that indicates the degree to which the circulation can be reduced by the sympathetic vasoconstrictor mechanism is very much needed in the study of peripheral vascular disorders.

Considerable interest is being displayed in the use of drugs that are sympatholytic—that is, capable of blocking sympathetic impulses, both as diagnostic tools and as therapeutic measures. Coller et al.²⁸ discuss their experiences with the use of tetraethyl ammonium chloride as an adjunct in the treatment of peripheral vascular disease and other painful states. Grimson and his associates²⁹ discuss the effects of priscol on peripheral vascular diseases, hypertension and circulation in patients.

In general, it can be stated that sympatholytic drugs vary in their blocking capacity, the duration of the effect, untoward side reactions and toxic manifestations. Furthermore, by contrast with procaine block or regional sympathectomy their action is diffuse and is not confined to the particular area of the vascular bed that one may be primarily interested in. Both in diagnosis and in therapy, one is concerned with increasing the blood flow to a certain area. This blood must be diverted from other areas for the maximal effect to be obtained. If only the vascular area in question is affected by therapy, the amount of blood borrowed from other areas will be comparatively slight. If many vascular areas are affected by therapy it is only reasonable to believe that the amount of blood diverted to the area in question will not be maximal. Consequently, the therapy will not be as effective. In this problem one is confronted with a considera-

close to, almost within, the spinal nerves. They varied in size, sometimes being apparent to the naked eye but more often being microscopic. These are referred to as intermediate ganglions. Skoog refers to Wrote's study of embryos, in which such ganglions were found principally in relation to the lumbar and brachial plexus, and sporadically in other segments. He considered that they arose from the sympathetic ganglions. Pick and Sheehan,⁵ in a detailed discussion of sympathetic ramus in man, also referred to ganglions placed upon the course of ramus as being surprisingly common, particularly in the lumbar region. Other studies of the anatomy of the lumbar chain^{6, 7} have emphasized the marked variations in the location of the lumbar ganglions themselves from person to person and on the two sides of the same person but did not describe these intermediate ganglions. From a practical point of view, the existence of intermediate ganglions would explain failure to denervate certain areas following conventional sympathectomies. It seems advisable to remove as much of the communicating ramus as possible in the performance of a sympathectomy. Under certain circumstances supplementary anterior-root section might be advisable.

Ray et al.⁸ have also made important observations concerning the origin of the sympathetic nerves to the pupil and upper extremity. By stimulating anterior roots during the course of laminectomies they have determined that the fibers to the pupil arise from the eighth cervical to the fourth dorsal segment, most commonly from the first to second dorsal. They also found that fibers to the upper extremity in man arise from the second to the ninth dorsal segment. In only 1 of 16 cases was there any outflow from the first dorsal segment. They found that if any one of the anterior roots from the second to the ninth dorsal was not divided, denervation of the upper extremity was incomplete. The usual technic for denervation of the upper extremity,⁹ which consists in division of the anterior roots of the second and third dorsal segments and usually the fourth dorsal, as well as section of the sympathetic trunk below the third or fourth dorsal, makes adequate provision for denervation of the upper extremity in most cases. It is apparent, however, that some residual activity may be expected in about 1 in 16 cases.

Grimson¹⁰ has demonstrated clearly that the vagus nerves do not carry pain sensation from the abdominal viscera since stimulation under spinal anesthesia did not cause abdominal pain. Ray and Neill¹¹ have demonstrated that thoracolumbar sympathectomy abolishes pain from the abdominal viscera, confirming in part the observations of Bentley and Smithwick.¹² It therefore seems clear that the pain relief that follows resection of the vagus nerves for peptic ulcer is not related to the

division of pain fibers. It is clear that these are contained within the splanchnic nerves.

Pick and Sheehan⁵ have demonstrated that the gray communicating rami are situated proximal to the white, at least in the thoracic region. Although of no clinical importance, this observation will necessitate the revision of the drawings in standard textbooks. The authors have also determined that the most common level of origin of the highest component of the great splanchnic nerve was the sixth thoracic ganglion. In 25 human dissections this branch arose from the sixth ganglion in 11, the seventh in 7, the eighth in 4 and above the sixth in 3 cases. This is in keeping with clinical experience. Since visceral fibers of consequence do not leave the great splanchnic nerve above the ninth or tenth thoracic level, these findings do not appear to lend support to current efforts to extend thoracolumbar sympathectomy in an upward direction in the treatment of hypertension.

Several careful studies of the anatomic arrangement of the vagus nerves in the supradiaphragmatic and infradiaphragmatic areas have been made.¹³⁻¹⁸ One gathers the impression that the fibers are indistinct in 10 to 15 per cent of cases and might easily be missed. The number of incomplete resections of the vagus nerves as judged by a secretory response to insulin hypoglycemia after operation, reported in the literature to date, approximates this figure. On anatomic grounds, the authors cited are equally divided concerning the best surgical approach to these nerves in the treatment of peptic ulcer. Half favor the transthoracic and half the transabdominal approach. Most surgeons experienced with both favor the latter, not only because it seems to be equally satisfactory from an anatomic point of view but also because it permits inspection of the lesion and supplementary gastric surgery if indicated. It is essential that surgeons appreciate all the anatomic variations of the vagus nerves if incomplete resections are to be reduced to a minimum. It is important also to realize that the identification of all the fibers of the vagus nerves depends to no small extent upon the surgeon's sense of touch.

PHYSIOLOGY

After resection of the vagus nerves, decreased peristalsis and delay in emptying of the stomach are regularly observed. These findings are apparent from both kymographic tracings¹⁷ and roentgenographic studies.¹⁸ In some cases motility may return toward normal in a few months. In others, abnormalities may exist for years.¹⁹ Emptying of the stomach may be delayed in the absence of pyloric obstruction owing either to stenosis or to pylorospasm. It appears to be caused by the intact sympathetic supply that inhibits the tone and peristalsis of the stomach and intestine. Peristalsis may be increased and emptying improved by the use of

in the dependent position after blanching has been induced by elevation of the extremity. If flushing begins in twenty seconds or less, one can be quite certain that the collateral circulation is adequate.

Sympathectomy for peripheral vascular disease is contraindicated, then, if the general cardiovascular status of the patient is poor or if the circulation of the extremity fails to improve after temporary interruption of its vasoconstrictor supply, except in cases in which there is adequate cooling of the digits in a cool environment associated with satisfactory collateral circulation. If sympathectomy is performed in poorly selected cases it will not only fail to improve the circulation but, as pointed out in recent years by Atlas³⁶ and Freeman,³⁷ may precipitate gangrene. Both these authors have reported cases in which the circulation of the foot was decreased after sympathectomy. They attributed this to the shunting of blood away from the capillary bed by the opening of arteriovenous shunts that followed sympathectomy. Freeman considered this most likely to occur in patients with low vascular tone. A study of his case reports suggests that while this may have been a factor, the history and symptoms indicated that a recent acute vascular occlusion occurred in 3 cases. The fourth had an injury to the foot, with fractured metatarsal bones. This suggests that the collateral circulation was inadequate at the time of operation. The 3 patients described by Atlas had poor collateral circulation, and 1 had an acute thrombosis of the femoral and popliteal arteries. The importance of an adequate collateral circulation as a prerequisite to sympathectomy in the presence of obliterative vascular disease of the main vessels cannot be overemphasized.

The recent development of satisfactory technics for more detailed clinical study of the circulation by plethysmography will no doubt further improve the selection of cases for sympathectomy. Apparatus designed by Burch³⁸ and Goetz³⁹ appears to be very satisfactory.

CAUSALGIA

Among the sequelae of penetrating wounds with injury to peripheral nerves is a remarkable symptom complex to which the term *causalgia* was applied by Mitchell, Moorhouse and Keen⁴⁰ in 1864. Their patients were soldiers in the Civil War, and their description of the symptom complex that certain persons develop after peripheral-nerve injuries is regarded as a classic. Recent discussions of this matter indicate that there are descriptions of the syndrome in the literature that antedated that referred to above but to which no name was applied. Until recent years, the cause and treatment of the disorder remained a mystery, and those who suffered from it were often regarded as having a psychosis or as being malingerers. Several years ago Homans⁴¹ wrote an excellent discussion of the

syndrome. He emphasized the role that the sympathetic nervous system played in the disorder and the efficacy of interrupting sympathetic pathways by procaine block or by sympathectomy as a therapeutic measure.

Every war has produced a new group of these cases, but it was not until World War II that effective therapy was available. The policy of concentrating cases that presented particular problems and required special treatment in surgical centers had much to do with their effective management. As a result, various reports emanating from these centers have done much to clarify the signs and symptoms and the proper management of such cases. Since examples of *causalgia* are seen from time to time among the civilian population it seems worth while to summarize the literature that has appeared as a result of the last war. Excellent discussions have been published by Spiegel and Milowsky,⁴² Mayfield and Devine,⁴³ Ulmer and Mayfield,⁴⁴ Allbritten and Maltby,⁴⁵ Rasmussen and Freedman,⁴⁶ Kirklin, Chenoweth and Murphy,⁴⁷ Freeman,⁴⁸ Shumacker^{49, 51} and White, Heroy and Goodman.⁵² These authors saw varying numbers of cases, and the interval between injury and treatment differed. There were variations in the signs and symptoms in the different groups, and certain features were emphasized particularly by some authors and to a lesser extent by others. It is possible, however, from these excellent discussions to obtain a fairly accurate composite picture of the problem as a whole.

Definition

Causalgia may be defined as a syndrome associated with a penetrating wound with a lesion of a peripheral nerve containing sensory fibers manifested by pain in the extremity, hand or foot primarily, that is accentuated by certain disturbing features in the patient's environment. The term should not be applied to allied post-traumatic disorders unassociated with penetrating wounds and peripheral-nerve injury.

Incidence

It is estimated that this syndrome develops in 2 to 5 per cent of peripheral-nerve injuries. It is not known why other persons with similar nerve injuries do not develop *causalgia*.

Onset

The pain apparently may begin immediately or within a few hours of injury. Perhaps 50 per cent of cases fall into this category. About 25 per cent of patients state that the pain begins in the course of a week, and about 15 per cent in the course of one to three weeks, and in the others it develops in the course of one to several months after injury.

tion of the relative merits of regional sympathectomy and more generalized sympathectomy both as diagnostic and as therapeutic measures De Bakey et al³⁰ have discussed the matter from this point of view and state

Peripheral vascular disease is characterized by a disturbance of, or actual diminution in, the normal amount of circulating blood which reaches the part, and its effective therapy is based on improvement in the circulation or an increase in the blood supply to the part. Therapeutic measures designed to produce dilatation of the entire vascular bed do not seem rational for a disease state localized to a single peripheral part, but, in spite of the illogic of the attempt, there are numerous reports concerning the production of generalized vasodilatation as a form of therapy for peripheral vascular disease involving portions of the body. The results of these efforts are open to question, theoretically such measures are inefficient. Moreover, even if an effective agent, i. e. with the ability to produce maximum vasodilatation, for this purpose did exist, its effect would be dangerous, the reaction would be shock-like, and the original purpose of increasing the blood supply to the local part would be completely defeated.

In view of the lack of rationale in peripheral vascular disease of the use of agents intended to produce generalized vasodilatation, quite aside from their ineffectiveness and theoretical dangers, the attention should be concentrated on measures which produce local vasodilatation. The best of these measures, in our experience, is sympathetic denervation of the affected part. It is rational because it conforms with the principles of hemodynamics just laid down, it produces local vasodilatation insuring maximum improvement in the local circulation of the diseased part. It is safe, because it does not reduce the arterial blood pressure or produce serious systemic disturbances by the sudden creation of a disproportion between the total volume of the vascular bed and the total blood volume. Finally, it is effective.

Indeed, we have yet to find a general vasodilator which could produce in a local part, such as the toes, fingers, foot, hand, or extremity, vasodilatation equal in degree or duration to that produced by sympathetic denervation of the part.

Important physiologic observations have been reported by Wilkins et al^{31, 32} concerning the vasomotor reaction of the visceral vascular bed. These have to do primarily with the problem of hypertension. For the first time, a method of study has been devised that permits one to tell to what extent the visceral vascular bed has been denervated. By means of optically recorded readings of blood pressure from the brachial or femoral artery they have shown that vasomotor responses following various stimuli are completely abolished after thorough denervation of the splanchnic bed but are not abolished after partial denervation of this area. This procedure will be helpful in judging the relative merits of various surgical technics in the treatment of hypertension and in the study of regeneration of sympathetic nerves to the viscera. It also has been useful in studying the effect of various drugs upon the visceral vascular bed.

CLINICAL APPLICATION

Obliterative Vascular Disease of the Lower Extremity

The fact that the circulation of an extremity can be improved by sympathectomy in the presence of known obliterative disease both of the arterio-

sclerotic variety and in patients having thromboangiitis obliterans is now quite generally recognized. The selection of patients for this form of therapy is of great importance. One must not only consider the extremity in question but also evaluate the cardiovascular status as a whole in arriving at a decision for or against sympathectomy. If evidence of severe cardiac, cerebral or renal involvement is detected, sympathectomy is contraindicated. The circulatory status of the extremity in question should always be subjected to detailed study before operation. Sympathectomy should never be performed without first obtaining evidence that the procedure is almost certain to be helpful. Of the methods of study available, temporary interruption of the sympathetic supply to the extremity by procaine block and the demonstration that a definite improvement in circulation results therefrom are commonly employed. De Takats et al³³ prefer paravertebral sympathetic block, and Cooper and Harris³⁴ use spinal anesthesia. Of the other methods of study, reflex vasodilatation by the Gibbon and Landis³⁵ technic and, more recently, the use of sympatholytic drugs should be mentioned. If any of these tests give definite evidence of temporary improvement in circulation one can be quite certain that the effect of operation will be worth while. As pointed out above, interruption of the sympathetic supply to the area in question by procaine block is likely to give more reliable information than tests that produce general vasodilatation. The latter may not cause an increase in blood flow to the extremity in question because of the shifting of blood to other areas where vasodilatation occurs more readily. The area being studied may even become cooler rather than warmer. This can lead the uninitiated to an erroneous conclusion concerning the advisability of sympathectomy. Not infrequently, this occurs in patients with a high degree of sympathetic tone in the extremity in question — in other words, in patients best suited for sympathectomy. It is wise not to attach the same significance to a negative as to a positive response to the tests mentioned. When the response is negative, one should be guided by the degree of cooling of the extremity in a cool environment — in other words, by evidence of the capacity of the vasoconstrictor mechanism to decrease blood flow through the extremity. It has been my experience that if the tips of the digits of the extremity in question cool to below 75°F after one hour's exposure to a room temperature of 68°F, and if the collateral circulation to the extremity is adequate, operation will be helpful. This conclusion is similar to that reached by Naide and Sayen²⁶ except that I prefer to study the extremity in question rather than to draw conclusions regarding the lower extremities from a study of the upper extremities only. The best simple test of collateral circulation is the time required for the tips of the digits to begin to flush

removed. Periarterial sympathectomy was found to be as ineffective as it has been in the past.

Mechanism of Pain

In spite of the fact that interruption of the sympathetic supply to an extremity almost always relieves causalgia, the mechanism for the production of pain and the explanation for its relief are not known. Some observers believe that the pain is caused by the stimulation of afferent somatic fibers at the point of peripheral-nerve injury by sympathetic efferents. This theory, which was proposed by Doupe, Cullen and Chance,⁵³ is in keeping with the explanation that failures following incomplete denervation of the site of injury could be due to the persistence of efferent sympathetic pathways having their synapses in intermediate rather than in the paravertebral ganglions. Other observers believe that the relief of pain is due to the interruption of afferent fibers carrying pain sensation from the extremities that pass through the sympathetic trunks and ganglions before entering the posterior roots to reach higher levels of pain perception. There has always been considerable doubt of the existence of such pathways from the extremities of man although some recent evidence has been presented by Treadgill⁵⁴ that they exist in animals. Whatever the explanation for causalgia may be, it is clear that sympathectomy is a very effective therapeutic measure.

ESSENTIAL AND MALIGNANT HYPERTENSION

In a discussion of early results of splanchnicectomy for hypertension de Takats⁵⁵ divides 250 cases followed one to six years into three groups designated as early, marked and too advanced respectively. There were 55 cases in the first, 171 in the second, and 24 in the third group. He regarded the results as satisfactory in 85 per cent of the first, in 75 per cent of the second, and in none of the third group. Failures in the first group were thought to be due to inadequate denervation in 2 cases, and were unexplained in 6. Failures in the second group were regarded as due to inadequate surgery in 5, heart failure in 7, and cerebral accidents in 6, and 13 cases were unexplained. All the failures in the third group were explained by poor case selection — that is, operation upon patients in a near-terminal stage of the disease.

Discussions of early results and the selection of cases for surgery have been reported by Hinton⁵⁶ and Smithwick.⁵⁷ The former based his discussion upon a series of 375 cases followed for six months to five years, and the latter upon a series of 439 cases followed for one to five years or more. In both papers, the circumstances under which the results were most likely to be unsatisfactory were discussed in considerable detail from the viewpoint of the individual patient. All these discussions must be regarded as preliminary, since no final evaluation

of the surgical treatment of hypertension can be made until an adequate number of cases have been followed for at least five years, and preferably longer. A study of early results is, however, worth while, since the obvious failures — namely, patients who fail to survive for more than a few years after operation — can be detected and eliminated as candidates for surgical treatment in the future.

So far only two articles have appeared in the literature in which the status of a sizeable number of surgically treated patients followed for five years or more has been discussed. Peet and Isberg⁵⁸ reported upon 437 cases followed for five to eleven years, and Smithwick⁵⁹ upon 256 cases followed for five to ten years. In both series the mortality rates compared favorably with those published for nonsurgically treated cases. In the latter series⁵⁹ the mortality rates for cases grouped according to the grade of eyegrounds was considerably lower than that reported by Keith, Wagener and Barker⁶⁰ for nonsurgically treated patients. The mortality rates for both sexes were considerably lower than those for nonsurgically treated patients reported by Janeway,⁶¹ Blackford, Bowers and Baker,⁶² Keith, Wagener and Barker⁶⁰ and Rasmussen and Boe.⁶³ The rates for cases when arranged by resting diastolic-blood-pressure levels were also much lower in the surgical series than in that reported by Rasmussen and Boe. The progress of cardiovascular disease as judged by the course of the electrocardiogram five years or more after operation compared very favorably with that of the nonsurgically treated patients reported by Canabal et al.,⁶⁴ as well as the cases reported by Rasmussen and Boe. The differences observed in this and the other comparisons referred to were large enough to be of statistical significance.

To date, nothing has appeared in the literature to give an adequate indication of the prognosis for a specific hypertensive patient whether untreated or treated medically or surgically. Such data should shortly be available for surgically treated patients followed for five to ten years and divided into subgroups in which the most important variable factors that exist in this disorder are held constant. It will then be possible to give a reasonably accurate prognosis for a particular patient. It is desirable that similar data be accumulated for nonsurgically treated patients so that more accurate comparisons can be made of the results of various therapeutic measures. This will be most helpful in the selection of the best form of therapy for a particular patient.

Articles have appeared relating to surgical technique.^{65, 66} These have to do primarily with extending the magnitude of operations for hypertension. The morbidity and mortality seem to be increased. It is doubtful whether the results will be improved sufficiently by more radical surgery to compensate for these untoward effects.

Nature

The pain is most frequently described as burning in nature. In some cases, however, no thermal characteristics are noted. In the great majority, about 90 per cent, it is constant. In occasional cases it is intermittent. The pain may be throbbing, aching, twisting, knife-like, stabbing or crushing, in addition to or instead of being burning. An essential feature of the pain is that it is intensified by various factors such as moving or touching the involved part, a sudden jarring of the bed, loud noise, emotional excitement, touching the part with slick objects such as sheets of paper or with a dry but not with a wet finger, touching the patient's body at any point, looking up in the air at high objects, extremes of temperature, or the sound of certain words such as paper or slick. Most of these stimuli are thought to cause increased sympathetic outflow to the extremity.

Distribution

The pain is most commonly associated with an incomplete injury of a peripheral nerve although there apparently are a few proved cases of causalgia following complete division of nerves. It is generally confined to or most intense in the sensory distribution of the nerve injury but may spread beyond the area.

Severity

The pain was slight in about 20 per cent, moderately intense in 35 per cent, severe in 35 per cent and excruciating in 10 per cent of the cases.

Nature of Nerve Injury

No characteristic lesion has been described. There is nothing different about the nerve injury that distinguishes it from identical injuries not associated with causalgia.

Vasomotor Manifestations

Two types of vasomotor changes are described, vasodilatation and vasoconstriction. In occasional cases the vasomotor status was regarded as normal. While it is possible that the original vasomotor status persists in a given case, the evidence suggests that vasodilatation may characterize the earlier stages of the disorder and may be replaced by vasoconstriction after a number of months. In the stage of vasodilatation the skin was usually pink, warm, dry, scaly and velvety, with increased growth of hair. In the stage of vasoconstriction the skin is described as being cold, thin, glistening and sweating profusely, with decreased growth of hair. Some form of moist dressing was preferred by most patients. In general, cool applications were preferred in the stage of vasodilatation, and warm in the stage of vasoconstriction.

Trophic Changes

So-called trophic changes in the skin, subcutaneous tissues, nails, joints and bones occurred frequently and apparently were closely related in both time of onset and severity to the intensity of the pain and the degree of disease. These changes were a serious handicap to rehabilitation once the pain was relieved. The importance of early diagnosis and treatment is repeatedly stressed.

Treatment

It seems generally agreed that therapy directed to the region of the nerve injury should not be the primary procedure unless some indication for exploration other than causalgia is present. Neurolysis rarely helped, and resection and suture only occasionally relieved the pain. All authors found that paravertebral procaine block of the sympathetic supply to the extremity resulted in complete or almost complete relief of pain in the great majority of cases. In some of the milder forms, one or several blocks resulted in cure. This applied to about 20 to 30 per cent of cases. In general it was noted that if the relief exceeded the duration of the anesthetic, treatment by blocking was apt to be successful. If the duration of relief corresponded to the duration of the anesthetic, one and a half hours or less, and if the relief on repeated blocking was the same or of shorter duration, this form of treatment was almost always unsuccessful. Under these circumstances, the extremity was sympathectomized. The results of sympathectomy in 75 per cent of the cases was excellent. In 20 per cent the result was good. Failures were reported in less than 5 per cent of cases. The upper extremity was involved in 60 per cent, and the lower in 40 per cent. In general, the results of the treatment were a little better in upper-extremity causalgias than in those of the lower extremity. The procedure most frequently utilized in denervation of the upper extremity was the so-called preganglionic section. This results in a more thorough denervation of the entire upper extremity than is obtained in the lower extremity after the conventional lumbar sympathectomy. This point, as well as the possible role of intermediate ganglions in explaining incomplete denervation of the thigh following operations of any magnitude upon the thoracolumbar chain, was emphasized above. Some authors believed the site of injury as well as the area of referred pain should be completely denervated. A few cases were reported in which extension of the sympathectomy upward for several segments, after failure to relieve lower-extremity causalgias that followed removal of the second and third or first, second and third lumbar ganglions, resulted in relief. In occasional cases, the pain was not relieved until thrombosed segments of arteries or aneurysms had been

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THE ULCER PROBLEM

Numerous reports of early experiences, both favorable and unfavorable, with resection of the vagus nerves alone and in combination with other operations upon the stomach continue to appear in the literature.⁶⁷⁻⁷³ Dragstedt et al.⁷⁴ correctly emphasize the need for special care in the postoperative management of these patients because of the marked disturbance of gastric motility that almost invariably occurs in the early postoperative period. Decompression of the stomach for several days after operation is essential. Feedings should consist of small quantities of clear fluids at first, with frequent estimations of gastric residue. Diet should be increased very gradually over a period of several weeks. If mechanical obstruction of the pylorus is apparent from the history, by x-ray study or by inspection of the lesion at operation, the authors believe that gastroenterostomy should be done at the time of the neurectomy. They regard their results to date as satisfactory and find no indications at present for gastric resection either alone or in combination with vagus resection in the treatment of duodenal ulcers requiring surgery.

Colp and his associates⁷⁵ compared the early results of subtotal gastrectomy alone and combined with vagus resection in two series of patients. The morbidity was increased by the combined procedure, but there was no mortality in either series. The combined procedure was much more effective in modifying both neurogenic and chemical gastric secretory mechanisms as judged by the effect upon gastric acidity. Achlorhydria was present in the fasting secretion as well as in response to food, insulin and histamine in a high percentage of the cases. If this persists, and if gastric acidity is as important as most observers believe it to be in the genesis and perpetuation of peptic ulcers, it seems likely that the combined procedure will lower the incidence of recurrent gastrojejunal ulceration. If it is not associated with a higher incidence of untoward side effects than radical gastrectomy alone, it may prove to be worth while.

To date, too few cases have been followed for an adequate period for one to reach any final conclusions regarding the relative merits of vagus resection alone, combined procedures and gastric resection only in the treatment of duodenal ulcers. Nothing but time combined with careful preoperative and postoperative studies can settle this problem. If there is any agreement upon any aspect of this matter, it seems to be the opinion of most that resection of the vagus nerves is particularly indicated in the management of gastrojejunal ulceration following subtotal gastrectomy. There is less agreement about the value of resection of the vagus nerves for gastrojejunal ulceration after gastroenterostomy. As a primary procedure, many believe that vagus resection combined with posterior gastroenterostomy is

justifiable in the management of obstructing or complicated ulcer problems when the risk of resection would be increased by difficulties encountered in the management of the duodenal stump, or in obstructed patients in extremely poor condition. Some surgeons believe that vagus resection may properly be combined with subtotal gastrectomy in patients whom experience has shown to be most susceptible to recurrent ulceration after subtotal gastrectomy alone — namely, those with recurrent hemorrhages and those with unusually high preoperative acidity. The frequency with which vagus resection alone may be considered varies greatly in different clinics. In some, so-called refractory nonobstructing ulcers seem to be quite common. In others, nonobstructing ulcers requiring surgical treatment are rare. One point upon which all authors are agreed is that the place resection of the vagus nerves will occupy in the management of duodenal ulcer is still in the investigative phase. It certainly has stimulated great interest in this subject and has resulted in much more careful study of each patient than was formerly the case. In the end, this can only react to the advantage of the ulcer patient.

Excellent reviews of surgery of the autonomic nervous system have recently been published by White,⁷⁶ Grimson⁷⁷ and Goetz.⁷⁸ These articles together cover almost every phase of the subject and contain extensive bibliographies.

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I had to anticipate a certain amount of criticism, perhaps, to the effect that the Society's office help and the salaried officials ought not to spend too much time or money or effort in the collection of this money. They are being paid to work for the Massachusetts Medical Society and not for the American Medical Association. That is a question, and I anticipated that criticism possibly by seeing to it that none of this work has been done by the officers or the salaried or wage-earning help of the Society.

The printing was done outside, and the American Medical Association paid the bill.

The mailing was done by a professional mailing concern, at the expense of the American Medical Association. And the checks, as they come back, are accounted for by an extra clerk, whose salary will be paid by the American Medical Association. So that all we have done is think about it and plan the routine of doing it. No real work has been subtracted from the time that we are supposed to be spending for the Massachusetts Medical Society.

The Secretary then moved that the Council ratify the action of the Executive Committee in this matter. The motion was seconded.

Dr Lawrence R. Dame (Franklin) emphasized the points brought out by the Secretary and reviewed the point of view of the Executive Committee.

Dr John J. Curley (Worcester North) stressed the fact that the American Medical Association had no available funds for an educational campaign and gave the point of view of the delegates that this was an emergency.

The President stated the question and suggested a vote by ballot. Dr Scarcello (Worcester) moved that the vote be taken by voice. The motion was seconded, and it was so voted. The President then put the question of ratification to a vote, and it was carried unanimously.

Committee on Public Relations—Dr Harold R. Kurth, Essex North, *Secretary*

Dr Kurth presented the report (Appendix No. 4) and moved its acceptance. The motion was seconded, and it was so voted.

Dr Kurth then stated there were two items in the report that required action by the Council. The first was the request of Dr Conlin to attend all committee meetings to gather information he might desire for the proper functioning of his office. As a result of discussion in the Executive Committee, Dr Kurth presented for approval the resolution appearing in the Executive Committee report as follows:

That the Director of Medical Education and Information shall be a non-voting member of all committees of the Massachusetts Medical Society. He shall be privileged to distribute the information acquired at such meetings after written approval of the Committee or its chairman, and further, if this action is approved, that it be referred to the Committee on By-laws and Council Rules for their action.

Dr Ralph R. Stratton (Middlesex East) made a motion to amend the resolution by inserting after the word "Committees," the words "with the exception of the Committee on Ethics and Discipline." This amendment to the resolution was seconded, and after some discussion it was so voted. The President then stated the resolution as amended, and it was so voted.

Dr Kurth then stated the second matter for consideration—namely, the code concerning matters of publicity so far as they concerned physicians and hospitals.

This code was submitted to the committee by Dr Conlin as it came from the Executive Committee of the Massachusetts Eye and Ear Infirmary. The Committee on Public Relations accepted the code as revised by the Committee on Ethics and Discipline, to which it had been referred. The Executive Committee believed that it should be resubmitted to the Committee on Ethics and Discipline for further consideration. Dr Kurth made a motion to resubmit the code. The motion was seconded.

Dr McCarthy (Norfolk) said he believed that the Society should have some control over certain publicity by hospitals. Dr Kurth stated that he believed that the Society could have no such control. The President stated the motion, and it was approved unanimously.

Dr Kurth moved for acceptance of the report as a whole, and it was so voted.

Committee on Legislation—Dr Solomon L. Skvirsky (Norfolk), *Chairman*

Dr David L. Belding (Norfolk South) presented the report (Appendix No. 5) in the absence of the chairman. Dr Belding made a motion that the Council approve the recommendation of the committee that the President annually appoint a subcommittee on national legislation, that all reports and actions of the subcommittee be cleared through the Committee on Legislation and that the President make such additional emergency and temporary appointments for handling national legislation as, in his opinion, the situation demands. The motion was seconded, and it was so voted.

Dr Belding then made a motion that the President appoint a committee of five to meet with the Massachusetts Nurses Association. The motion was seconded, and it was so voted. Dr Belding moved acceptance of the report as a whole. The motion was seconded, and it was so voted.

Committee on Arrangements—Dr Harold G. Giddings (Middlesex South), *Chairman*

Dr Giddings presented the report (Appendix No. 6) as informational and moved its acceptance. The motion was seconded, and it was so voted.

MASSACHUSETTS MEDICAL SOCIETY

PROCEEDINGS OF THE COUNCIL

Stated Meeting, February 2, 1949

A STATED meeting of the Council was called to order by the president, Dr Daniel B Reardon, Norfolk South, on Wednesday, February 2, 1949, at 10 30 a m in John Ware Hall, 8 Fenway, Boston

Two hundred and thirty-four councilors (Appendix No 1) were present

The President then announced the following appointments

To the Section on Pathology and Physiology

Dr Monroe J Schlesinger, *Chairman*

Dr Donald A Nickerson, *Secretary*

To the Council

Dr Joseph P Marnane, Worcester North

To the Committee to Meet with the Officers of the Bay State Medical Rehabilitation Clinic

Dr Alexander P Aitken

The President asked for approval of these appointments, and it was so ordered by vote of the Council

The Secretary presented the record of the October 6, 1948, meeting of the Council as published in the *New England Journal of Medicine*, issue of December 2, 1948, and moved its acceptance The motion was seconded, and it was so ordered by vote of the Council

REPORTS OF COMMITTEES

Executive Committee—Dr H Quimby Gallupe, Middlesex South, *Secretary*

The Secretary presented the minutes of the meeting of the Executive Committee held on January 5, 1949, as mimeographed (Appendix No 2) and mailed to the councilors He drew the attention of the councilors to the change of time of the committee meeting, the length of it and the expanded report of discussions

The Secretary then presented the report of the Committee on Membership (Appendix No 3) and moved the approval of the recommendation concerning new categories of membership The motion was seconded, and it was so voted without discussion

The Secretary then said that there had been no business referred to the Committee by the Council and that there was only one matter of new business—namely, that concerning the American Medical Association assessment He reviewed the information concerning this as follows

Immediately following the Interim Session of the American Medical Association in St. Louis on December 1, I received the following telegram from the Secretary of the American Medical Association

Recent Interim Session House of Delegates unanimously decided to assess each member of American Medical Association \$25 00 You are requested to collect this assessment through your county units or any other way you desire Bill association for any extra expense in connection with the collection

That seemed to be rather a big job for the secretary of this society to do all by himself and without any particular authority from this society to act My first attempt was to find out if this assessment by the American Medical Association was proper, according to their by-laws, and I can assure you that it is, so far as we are aware, because last summer at the annual session of the American Medical Association that organization produced new by-laws, which were accepted by the House of Delegates, Article 2 of which reads

Funds may be raised by an equal assessment of dues of not more than \$25 annually on each of the active members on recommendation by the Board of Trustees and after approval by the House of Delegates

I then approached the delegates of the Society who had attended the Interim Session I was at St. Louis myself, but did not attend the meeting of the House of Delegates. I was there for another purpose

Our delegates assured me that they did vote unanimously for this assessment and that they did so because the American Medical Association was without funds and had been for some time, that last year the American Medical Association had gone into the red by a considerable number of thousands of dollars, and that all their money came from subscriptions to their various journals, some of which operated in the red

They were assured that this assessment was decided upon by the trustees of the American Medical Association previous to November 2, when Mr Truman was elected It was not influenced particularly by politics or proposed legislation in the Eighty-First Congress The money was needed anyway, and our delegates assured us that it was their complete understanding that this assessment was necessary There was a certain amount of emergency to it, and it was their understanding that it was completely voluntary and that no penalty could be dealt to anyone not subscribing to this assessment

Now, our delegates are unanimous on that opinion, and as you well know, I have stated that publicly It is the opinion of the officers of the Society that that is the story and there is nothing in the by-laws of the Society that makes it possible to punish anybody for not paying an American Medical Association assessment Therefore, it seems logical to believe that it is voluntary and I am certain that the Society and the American Medical Association do not want your money or anybody else's money if it is not given voluntarily

I am trying, as you can see, to answer any of the questions that have been raised concerning the issue over the last two months

Having decided that that was the whole story, I still was not willing to act as an agent of the American Medical Association without some degree of authority from the Society and I did not think it was wise to wait for a Council meeting I made the proposal to the Executive Committee that they authorize me to act as an agent for the American Medical Association in the collection of this money, and they did so unanimously, after first voting that this was an emergency, under the by-laws the Executive Committee has the right to authorize any officer of the Society to act in an emergency So the Executive Committee acted within their rights, and after careful discussion, which lasted a considerable time, they voted unanimously to do what the American Medical Association requested me to do

I was asked yesterday by one of our officers to summarize what has happened since I might say first that the bill that you received and the method of producing it were decided upon by a meeting of our delegates and the officers of the Society, and they all agreed that the method of sending the bill, the printed material that you saw on it, was all right. That vote was unanimous.

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Dr Ralph R. Stratton (Middlesex East) made a motion to amend the resolution by inserting after the word "Committees," the words "with the exception of the Committee on Ethics and Discipline." This amendment to the resolution was seconded, and after some discussion it was so voted. The President then stated the resolution as amended, and it was so voted.

Dr Kurth then stated the second matter for consideration—namely, the code concerning matters of publicity so far as they concerned physicians and hospitals.

This code was submitted to the committee by Dr Conlin as it came from the Executive Committee of the Massachusetts Eye and Ear Infirmary. The Committee on Public Relations accepted the code as revised by the Committee on Ethics and Discipline, to which it had been referred. The Executive Committee believed that it should be resubmitted to the Committee on Ethics and Discipline for further consideration. Dr Kurth made a motion to resubmit the code. The motion was seconded.

Dr McCarthy (Norfolk) said he believed that the Society should have some control over certain publicity by hospitals. Dr Kurth stated that he believed that the Society could have no such control. The President stated the motion, and it was approved unanimously.

Dr Kurth moved for acceptance of the report as a whole, and it was so voted.

Committee on Legislation—Dr Solomon L. Skvirsky (Norfolk), *Chairman*

Dr David L. Belding (Norfolk South) presented the report (Appendix No. 5) in the absence of the chairman. Dr Belding made a motion that the Council approve the recommendation of the committee that the President annually appoint a subcommittee on national legislation, that all reports and actions of the subcommittee be cleared through the Committee on Legislation and that the President make such additional emergency and temporary appointments for handling national legislation as, in his opinion, the situation demands. The motion was seconded, and it was so voted.

Dr Belding then made a motion that the President appoint a committee of five to meet with the Massachusetts Nurses Association. The motion was seconded, and it was so voted. Dr Belding moved acceptance of the report as a whole. The motion was seconded, and it was so voted.

Committee on Arrangements—Dr Harold G. Giddings (Middlesex South), *Chairman*

Dr Giddings presented the report (Appendix No. 6) as informational and moved its acceptance. The motion was seconded, and it was so voted.

*Committee on Finance — Dr Robert W Buck
(Middlesex South), Chairman*

Dr Buck presented the report as printed (Appendix No 7) and moved the adoption of the first recommendation as follows

An increase of \$1500 in the salary of the Director of Medical Information and Education above that provided in your action last year by which annual increases were to amount to \$500 each year until a total salary of \$10,000 was reached. It is the opinion of the officers of the Society, the members of the original committee that chose the Director and of other representative fellows that the full salary should be paid beginning in 1949 instead of in 1952

The motion was seconded, and it was so voted

Dr Buck moved the adoption of the second recommendation as follows

I move an increase of \$1200 in the salary of the Executive Secretary, which has been requested by officers of the Society, and approved by your committee and also approved by the Executive Committee.

The motion was seconded, and it was so voted

Dr Buck then moved that the salary of the Assistant Treasurer be fixed at \$500 (no salary had been paid previously). The motion was seconded, and it was so voted

Dr Buck then moved that the Director of Medical Information and Education be provided with secretarial service at an annual cost of \$2,000. The motion was seconded, and it was so voted

Dr Buck then moved "that the increase in the budget for the Committee on Legislation be adopted, with the explanation that this increase will largely be demanded because of increased secretarial duties that will be required." The motion was seconded, and it was so voted

Dr Buck then spoke as follows

I only wish to call attention to the last paragraph and perhaps emphasize it. We have found no difficulty in using up the additional funds that have been supplied by the increase in dues. There have been so many requests and apparent real needs for the use of these funds that it becomes a little too easy to spend money. We must now realize that we have reached almost the limit of our possible expansion and that it is now up to the chairmen of all committees and to all of us to realize that we are working within our budget, but not with any great margin to spare and nobody wants to see another increase in dues or have to raise money from some other source

Dr Buck then made the motion to accept the report as a whole. The motion was seconded, and it was so voted

Committee on Industrial Health — Dr Daniel L Lynch (Norfolk), Chairman

Dr Lynch presented the report (Appendix No 8) as informational and moved its acceptance. The motion was seconded, and it was so voted

Advisory Subcommittee on Malpractice Insurance — Dr Carl Bearse (Norfolk), Chairman

Dr Bearse submitted his report (Appendix No 9) with one correction — that is, 155 suits pending in-

stead of 147. He added that during 1947 there were 64 new suits entered in courts. Dr Bearse stated that his committee had sent questionnaires to 5530 doctors, letters were sent to 49 secretaries of medical organizations and to all companies writing malpractice insurance in Massachusetts

Dr Bearse made the motion that the Council approve the recommendation concerning "listeners." The motion was seconded. Dr John Curley stated the arguments against the motion as discussed in the Executive Committee. Dr McCarthy (Norfolk) spoke in favor of the motion. Dr Dame (Franklin) spoke against the motion. Dr Allan M Butler (Suffolk) pointed out that either the doctor or the insurance company could employ "listeners" if they wished

The President stated the motion, and it was not carried by voice vote

Dr Bearse then made a motion to approve the second recommendation concerning a panel of experts. The motion was seconded. There was no discussion. On voice vote the motion was defeated

Dr Bearse then made a motion that the Council approve the third recommendation that his committee review the testimony of members and that if the testimony were found substandard, the matter would be reported to the Committee on Ethics and Discipline. The motion was duly seconded, and it was so voted

Dr Bearse then moved that the Council approve the fourth recommendation that the insurance companies be notified of the actions of the Council in these matters. The motion was seconded

Dr Kickham (Norfolk) said he believed there was no necessity for the Council to report its actions to any insurance company. On a show of hands the motion was lost

Dr Bearse then moved for acceptance of the report as a whole. This motion was seconded, and it was so voted

The Secretary called the attention of the Council to the recommendation of the Executive Committee praising the committee for the good job it had done and hoping that it would continue to act. The Secretary moved the approval of this recommendation by the Council. The motion was seconded, and it was so voted

Committee on Emergency Medical Service — Dr Reginald Fitz (Suffolk), Chairman

In the absence of the Chairman, the Secretary submitted the report (Appendix No 10) and stated the arguments of the Executive Committee against the recommendations of the committee concerning the make-up of the committee as proposed. The Secretary made the motion that the recommendation of the Committee on Emergency Medical Service be disapproved by the Council. This motion was seconded

Dr Scarcello (Worcester) stated that he believed the committee should be a representative committee like the committees on Public Relations and Legislation

Dr Curley (Worcester North) said he believed that a group near Boston would be most effective and that if the chairman of the district committees were added to the present committee, the resulting enlarged committee would be democratic. On a show of hands, the motion to disapprove was carried.

The Secretary made a motion to approve the recommendation of the Executive Committee, which would add the chairmen of the district committees to the present committee. The motion was duly seconded, and it was so voted. The Secretary moved for acceptance of the report as a whole. The motion was seconded, and it was so voted.

Committee to Meet with the Officers of the Bay State Rehabilitation Clinic—Dr Charles H. Bradford (Suffolk), *Chairman*

Dr Bradford made the motion to approve the report (Appendix No. 11) as a whole, with its four recommendations. The motion was seconded, and it was so voted.

The President stated that he was reappointing the same committee as the now working committee and adding to it Dr Alexander P. Aitken. He asked for approval of this action. The motion was seconded, and it was so voted.

Advisory Subcommittee on Medical Education—Dr I. R. Jankelson (Norfolk), *Chairman*

Dr Jankelson made a motion to accept the report (Appendix No. 12) as informational. The motion was seconded, and it was so voted.

Committee on Diabetes—Dr Howard F. Root (Suffolk), *Chairman*

Dr Root presented the first part of the report, as printed in the Circular of Advance Information (Appendix No. 13), as informational and moved its acceptance. The motion was seconded, and it was so voted. Dr Root then moved for the approval of the resolution in the supplementary report (Appendix No. 14). The motion was seconded, and it was so voted. Dr Root then moved acceptance of the report as a whole. The motion was seconded, and it was so voted.

Committee on Blue Cross-Blue Shield Problems—Dr Charles J. E. Kickham (Norfolk), *Chairman*

Dr Kickham presented the report (Appendix No. 15) as printed. He moved that the first recommendations to have the President appoint annually a general chairman of the Blue Shield Fee Committee. Chairmen be approved by the Council. The motion was seconded, and it was so voted. Dr Kickham then moved that the second recommendation, "that the Executive Director of Blue Shield annually re-

quest the Specialty Sections within the Society and the Specialty Sections without the Society to review the composition of their respective Blue Shield Fee Committees and that the Executive Director of Blue Shield suggests to the Specialty Sections a uniform method of rotating membership on Blue Shield Fee Committees," be approved by the Council. The motion was seconded, and it was so voted. Dr Kickham then moved acceptance of the report as a whole. The motion was seconded, and it was so voted.

Committee on By-Laws and Council Rules—Dr Edward P. Bagg (Hampden), *Chairman*

Dr Bagg presented the report of the committee (Appendix No. 16) as corrected. Dr Bagg made a motion to accept the report as a whole. The motion was seconded, and it was so voted. Dr Bagg then made a motion for the approval by the Council of each of the resolutions in the report. The motions were each seconded, and it was so voted.

Dr Bagg made a motion for approval by the Council of the changes in the Council rules as printed. The motion was seconded, and it was so voted.

Dr Bagg then made a motion for the approval of the preamble to the Rules. The motion was seconded, and it was so voted. Dr Bagg then moved for approval of the report as a whole. The motion was seconded, and it was so voted.

Advisory Committee to the Woman's Auxiliary—Dr John F. Conlin (Suffolk), *Chairman*

Dr Conlin submitted the report (Appendix No. 17) as informational and moved its acceptance. The motion was seconded, and it was so voted.

Dr Conlin then made the following statement:

An additional progress report concerning the Woman's Auxiliary points to 16 of the 18 district medical societies that have now approved the formation of auxiliaries. Eleven of the auxiliaries are now formed, and 2 more are in process of formation.

It is fondly hoped that this portion of our activities will be an accomplished fact by the time of the annual meeting.

I respectfully request officers of the district medical societies, and in particular district advisory committees, to take a strong interest, particularly at this time, in the matter of the auxiliaries, and to render them every possible assistance in the formation and extension of membership and in their various programming and other activities. I point out that in some instances there are minor difficulties, and I ask that the advisory committees be alert, and remember that they have a veto power, upon actions of the auxiliaries that bear upon major matters in the field of, particularly, public relations and legislation.

Consequently, any major project of theirs must be approved by the local advisory committees. It is a matter of extreme importance that that be closely observed, not that malicious mistakes be made, but that mistakes due to lack of knowledge do not occur.

As with any new project, there are a few minor difficulties. There is the question of proper representation of various towns throughout a district. Occasionally, there is some suggestion of factionalism and minor matters of that type, but I see no major difficulty.

I conclude my report with the observation that not only is the Auxiliary doing everything that we fondly hoped

Committee on Finance — Dr Robert W Buck (Middlesex South), *Chairman*

Dr Buck presented the report as printed (Appendix No 7) and moved the adoption of the first recommendation as follows

An increase of \$1500 in the salary of the Director of Medical Information and Education above that provided in your action last year by which annual increases were to amount to \$500 each year until a total salary of \$10,000 was reached. It is the opinion of the officers of the Society, the members of the original committee that chose the Director and of other representative fellows that the full salary should be paid beginning in 1949 instead of in 1952

The motion was seconded, and it was so voted

Dr Buck moved the adoption of the second recommendation as follows

I move an increase of \$1200 in the salary of the Executive Secretary, which has been requested by officers of the Society, and approved by your committee and also approved by the Executive Committee.

The motion was seconded, and it was so voted

Dr Buck then moved that the salary of the Assistant Treasurer be fixed at \$500 (no salary had been paid previously). The motion was seconded, and it was so voted

Dr Buck then moved that the Director of Medical Information and Education be provided with secretarial service at an annual cost of \$2,000. The motion was seconded, and it was so voted

Dr Buck then moved "that the increase in the budget for the Committee on Legislation be adopted, with the explanation that this increase will largely be demanded because of increased secretarial duties that will be required". The motion was seconded, and it was so voted

Dr Buck then spoke as follows

I only wish to call attention to the last paragraph and perhaps emphasize it. We have found no difficulty in using up the additional funds that have been supplied by the increase in dues. There have been so many requests and apparent real needs for the use of these funds that it becomes a little too easy to spend money. We must now realize that we have reached almost the limit of our possible expansion and that it is now up to the chairmen of all committees and to all of us to realize that we are working within our budget, but not with any great margin to spare and nobody wants to see another increase in dues or have to raise money from some other source

Dr Buck then made the motion to accept the report as a whole. The motion was seconded, and it was so voted

Committee on Industrial Health — Dr Daniel L Lynch (Norfolk), *Chairman*

Dr Lynch presented the report (Appendix No 8) as informational and moved its acceptance. The motion was seconded, and it was so voted

Advisory Subcommittee on Malpractice Insurance — Dr Carl Bearse (Norfolk), *Chairman*

Dr Bearse submitted his report (Appendix No 9) with one correction — that is, 155 suits pending in-

stead of 147. He added that during 1947 there were 64 new suits entered in courts. Dr Bearse stated that his committee had sent questionnaires to 5530 doctors, letters were sent to 49 secretaries of medical organizations and to all companies writing malpractice insurance in Massachusetts

Dr Bearse made the motion that the Council approve the recommendation concerning "listeners". The motion was seconded. Dr John Curley stated the arguments against the motion as discussed in the Executive Committee. Dr McCarthy (Norfolk) spoke in favor of the motion. Dr Dame (Franklin) spoke against the motion. Dr Allan M Butler (Suffolk) pointed out that either the doctor or the insurance company could employ "listeners" if they wished

The President stated the motion, and it was not carried by voice vote

Dr Bearse then made a motion to approve the second recommendation concerning a panel of experts. The motion was seconded. There was no discussion. On voice vote the motion was defeated

Dr Bearse then made a motion that the Council approve the third recommendation that his committee review the testimony of members and that if the testimony were found substandard, the matter would be reported to the Committee on Ethics and Discipline. The motion was duly seconded, and it was so voted

Dr Bearse then moved that the Council approve the fourth recommendation that the insurance companies be notified of the actions of the Council in these matters. The motion was seconded

Dr Kickham (Norfolk) said he believed there was no necessity for the Council to report its actions to any insurance company. On a show of hands the motion was lost

Dr Bearse then moved for acceptance of the report as a whole. This motion was seconded, and it was so voted

The Secretary called the attention of the Council to the recommendation of the Executive Committee praising the committee for the good job it had done and hoping that it would continue to act. The Secretary moved the approval of this recommendation by the Council. The motion was seconded, and it was so voted

Committee on Emergency Medical Service — Dr Reginald Fitz (Suffolk), *Chairman*

In the absence of the Chairman, the Secretary submitted the report (Appendix No 10) and stated the arguments of the Executive Committee against the recommendations of the committee concerning the make-up of the committee as proposed. The Secretary made the motion that the recommendation of the Committee on Emergency Medical Service be disapproved by the Council. This motion was seconded

ferred to the Committee on Public Health. The motion was seconded, and it was so voted.

Dr B E Barton (Norfolk) said that to further the Gallupe Plan and other purposes it is desirable to have every eligible practitioner enrolled in the Society. He said that at a pre-Council meeting of the councilors of the Norfolk District Society, the following resolution was passed: "That the Massachusetts Medical Society be informed that the Norfolk District favors placing before the Council for its consideration the matter of contacting eligible nonmembers of the Society to see if they would be interested in becoming members." Dr Barton moved acceptance of the resolution. The motion was seconded, and it was so voted.

The President recognized Dr Earle M Chapman (Suffolk), who made the following remarks:

I come before the Council as a representative of a group of earnest younger men in medicine who have met and discussed these problems that we are faced with and they have asked me to present these as their expression of their ideas on the current problems, so I should like to bring this up for consideration.

First, we believe that the health of the people served by prepayment insurance plans will be most benefited by medical care free of Government administration and control.

Secondly, we should like to call attention to the profligate waste and duplication in health programs operated by the Government in both hospital beds and personnel, as reported by the Hoover Commission. We believe that compulsory health insurance operated by the Government would result in similar inefficiencies.

Thirdly, the manner of expression of policy on the part of the American Medical Association has served to diminish public confidence in that body, to the serious concern of many of the members of the Association.

Therefore, we suggest as constructive proposals, worthy of support, the following:

First, unqualified endorsement of the principles for distribution of medical care agreed upon by the National Health Assembly in Washington, D C, in May of 1948. And specifically within that body of principles, we endorse the action of the Massachusetts Medical Society in promoting, one, the rapid expansion of a voluntary medical care prepayment plans to provide more comprehensive enrollment. We appreciate that it will be necessary to use tax funds to extend such services to income groups financially unable to secure such benefits.

And secondly that benefits under these prepayment plans be expanded to provide more comprehensive coverage for illness. Implicit in this expansion should be the principle of the assumption of a portion of the initial cost of any one illness by the subscriber.

We further urge that our delegates to the American Medical Association be instructed to press for the general adoption of the above principles and proposals by the American Medical Association.

Dr Leland S McKittrick (Suffolk) was recognized and spoke as follows:

Dr Chapman was good enough to give me a copy of these suggestions and I have been thinking them over. I should like to say at the outset that I am not only sympathetic with but also enthusiastic for the thinking and the initiative that is behind these suggestions.

I am perfectly sure that, without a great deal of thought and a great deal of discussion, there are certain things in the suggestions that we would find it difficult to approve. I could not possibly approve, for example, of unqualified endorsement of the principles for the distribution of medi-

cal care agreed upon by the National Health Assembly in Washington. There are certain things that I would want to go over very carefully. But I think that the thinking behind this might well represent something that we could give careful thought to, and the suggestion I have is this:

I wonder — and I am not going to make it in the form of a motion because I do not know whether it is a proper thing to do or not, whether it would be agreeable to Dr Chapman and whether the Council would like it — but the suggestion is that this be referred to the Committee on Economics, with the request that it be given careful thought, and that they bring back and send to the Council some concrete suggestions in keeping with the thinking behind this communication.

In other words, it is about time that the Committee on Economics got to work again. I think, as a matter of fact, that we have some principles that the Council has agreed upon, which are far better than the National Assembly endorsement that is asked for here. It is possible that the Council and the Society have already proved that concrete suggestions might be brought back that the delegates could take to Atlantic City with them.

At any rate, I think it is worth a good deal of careful consideration and probably several long, hard meetings to try to come up with something. And that would be my suggestion as a possible mechanism of handling this communication.

Dr McKittrick moved that this be referred to the Committee on Medical Economics. The motion was seconded.

Dr Faxon and Dr Bagnall endorsed the substance of Dr Chapman's proposals. Dr Bagnall said he would like to have the group discussing this matter enlarged to include the Society's delegates and Dr Chapman's group. Dr Norman A Welch suggested that the matter might be one of public relations rather than economics. Dr Curley moved the following amendment to the motion: "That the matter be referred to a joint meeting of the Committees on Medical Economics and Public Relations." The motion was seconded, and it was so voted. The President called for a vote on the motion as amended. It was so voted. Dr Bagnall said that all interested parties would be invited and set the time of the meeting as Wednesday, February 9, 1949.

A motion to adjourn was made and seconded, and it was so voted at 3 00 p m.

H QUIMBY GALLUPE, *Secretary*

APPENDIX NO 1

ATTENDANCE OF COUNCILORS

BERKSHIRE	R E Blais
Modestino Criscitiello	J A Bradley
P J Sullivan	N F DeCesare
	A P George
BRISTOL NORTH	H R Kurth
J V Chatigny	R C Norris
W E Dawson	L C Peirce
J L Murphy	F W Snow
W M Stobbs	C T Stokes
	F N Sweetser
	C A Weiss
BRISTOL SOUTH	
J C Corrigan	
D F Gallery	
R H Goodwin	
William Mason	
C C Tripp	
ESSEX NORTH	
M F Ames	
E S Bagnall	
	ESSEX SOUTH
	S N Gardner
	Loring Grimes
	C A Herrick
	P P Johnson
	R T Moulton
	A E Parkhurst
	W G Phippen

it would do but also the Auxiliary as a whole, as now constituted, is doing an excellent job and we expect a tremendous amount from it in the immediate future

Report of the Meeting of the House of Delegates of the American Medical Association — Dr Walter G Phippen (Essex South)

Dr Phippen made the following statement

This report is merely informational. You will find it on the last two and a half pages of the Circular of Advance Information (pages 30, 31 and 32). If there is any question anyone wishes to ask, I should be very glad to answer it.

I should like to say that your delegates to the House of Delegates would be very glad to receive any information or any criticism that you have, or to be instructed in any way you would like to have them vote. Remember, always, that they are your servants and try to act exactly as you would like to have them act.

The House of Delegates is a serious body. It consists of 175 members elected by the different constituent state societies, in addition to 1 member from each section of scientific assembly, and 1 member each from the Army, Navy and Public Health Service. The meetings are extremely well attended. The work is all conducted in a business-like way. The resolutions are presented to the House and are then handed to reference committees. These reference committees are chosen before the House sits, so that the men know on which committee they are going to serve.

At the appointed time these reference committees hold hearings at which anyone is invited to come and talk — not necessarily members of the House of Delegates, not necessarily entirely members of the American Medical Association, but anyone may come to a meeting of a reference committee and express his views.

After the reference committees have heard all the evidence they sit sometimes for long hours, sometimes well after midnight, discussing the questions that they have before them, and drawing up a report.

This report is then presented to the full House of Delegates and is open for debate, which is often lively and spirited.

I can assure you that, contrary to the belief of some people, the House of Delegates is really a representative body. You meet there people from all over the country. You may sit beside a man from Texas at breakfast and a man from Oregon at lunch, and you learn the very diversified opinions that are prevailing all over the country.

Your delegates propose to hold a meeting some weeks before the meetings of the House of Delegates so that they may discuss the problems that are of interest to you.

Dr Phippen then made a motion to accept the report. The motion was seconded, and it was so voted.

The Secretary then made a motion to accept the report of the Executive Committee as amended. The motion was seconded, and it was so voted. The Secretary then moved to recess until 2 00 p m. The motion was seconded, and it was so voted.

After the Cotting Luncheon, the Council was called to order by the President at 2 00 p m.

The Secretary stated that under unfinished business was the report of the Committee on Tax-Supported Medical Care, which had been laid on the table at the meeting of October 6, 1948.

Dr A J A Campbell (Suffolk) made a motion that this report be taken off the table. The motion was seconded, and it was so voted.

Dr Albert A Hornor (Suffolk) stated that the question of tax-supported medical care was still confused and that his committee needed more data.

He made the motion that the matter be referred back to the committee for a report at the annual meeting. The motion was seconded, and it was so voted.

The Secretary stated that under unfinished business was the matter of voluntary registration of cancer, recommended by the Committee on Cancer, which had been laid on the table at the October 6, 1948, meeting. The Secretary moved that the following motion be taken off the table.

It is therefore recommended by the Committee on Cancer that the Massachusetts Medical Society endorse the principle of voluntary registration of cancer cases, and that the Committee on Cancer be instructed to develop a system for consideration by the Council.

The motion was seconded, and it was so voted.

Dr Thomas J Anglem (Suffolk) made a motion to approve the above recommendation for the following reasons:

The nature of the disease is such that everyone accepts the fact that long-term study and statistical analysis of large groups of cases is essential, and we believe that the centralization of registration in some one area or place would definitely facilitate this type of study. At present, the cases are buried in the files of various hospitals, and anyone attempting to do a large-scale study is working against difficult odds.

Moreover, we believe that this type of registration would uncover and identify cases that are now being lost. The large number of cases that are seen by the family doctor in advanced or moderately advanced stages of the disease that are not now registered anywhere would be uncovered by this type of registration. And we also believe that anything that focuses further attention on the disease has educational value.

The motion was seconded.

Dr Charles C Lund and Dr Vlado A Getting spoke in favor of the motion. Dr Getting offered the following amendment to the motion: "That the first portion of endorsing voluntary registration be omitted and that the motion read that the 'Committee on Cancer of the Massachusetts Medical Society be authorized to make a study and present a plan to the Council for voluntary registration of Cancer'."

The motion was seconded, and it was so voted. The President then called for a vote on the motion as amended. It was so voted.

Dr Anglem moved the acceptance of the report as amended. The motion was seconded, and it was so voted.

The Secretary said that under new business Dr Root had sent a letter to the President recommending that the matter of diabetes detection among industrial groups be studied. The Secretary moved that this matter be referred to the Committee on Diabetes. The motion was seconded, and it was so voted.

The Secretary stated that he had received a letter from the Massachusetts Society of Clinical Psychologists concerning the problem of registering clinical psychologists as assistants in the practice of psychiatry. The Secretary moved that this matter be re-

ferred to the Committee on Public Health. The motion was seconded, and it was so voted.

Dr B E Barton (Norfolk) said that to further the Gallupe Plan and other purposes it is desirable to have every eligible practitioner enrolled in the Society. He said that at a pre-Council meeting of the councilors of the Norfolk District Society, the following resolution was passed: "That the Massachusetts Medical Society be informed that the Norfolk District favors placing before the Council for its consideration the matter of contacting eligible nonmembers of the Society to see if they would be interested in becoming members." Dr Barton moved acceptance of the resolution. The motion was seconded, and it was so voted.

The President recognized Dr Earle M Chapman (Suffolk), who made the following remarks:

I come before the Council as a representative of a group of earnest younger men in medicine who have met and discussed these problems that we are faced with and they have asked me to present these as their expression of their ideas on the current problems, so I should like to bring this up for consideration.

First, we believe that the health of the people served by prepayment insurance plans will be most benefited by medical care free of Government administration and control.

Secondly, we should like to call attention to the profligate waste and duplication in health programs operated by the Government in both hospital beds and personnel, as reported by the Hoover Commission. We believe that compulsory health insurance operated by the Government would result in similar inefficiencies.

Thirdly, the manner of expression of policy on the part of the American Medical Association has served to diminish public confidence in that body, to the serious concern of many of the members of the Association.

Therefore, we suggest as constructive proposals, worthy of support, the following:

First, unqualified endorsement of the principles for distribution of medical care agreed upon by the National Health Assembly in Washington, D C, in May of 1948. And specifically within that body of principles, we endorse the action of the Massachusetts Medical Society in promoting, one, the rapid expansion of voluntary medical care prepayment plans to provide more comprehensive enrollment. We appreciate that it will be necessary to use tax funds to extend such services to income groups financially unable to secure such benefits.

And secondly that benefits under these prepayment plans be expanded to provide more comprehensive coverage for illness. Implicit in this expansion should be the principle of the assumption of a portion of the initial cost of any one illness by the subscriber.

We further urge that our delegates to the American Medical Association be instructed to press for the general adoption of the above principles and proposals by the American Medical Association.

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In other words, it is about time that the Committee on Economics got to work again. I think, as a matter of fact, that we have some principles that the Council has agreed upon, which are far better than the National Assembly endorsement that is asked for here. It is possible that the Council and the Society have already proved that concrete suggestions might be brought back that the delegates could take to Atlantic City with them.

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Dr McKittrick moved that this be referred to the Committee on Medical Economics. The motion was seconded.

Dr Faxon and Dr Bagnall endorsed the substance of Dr Chapman's proposals. Dr Bagnall said he would like to have the group discussing this matter enlarged to include the Society's delegates and Dr Chapman's group. Dr Norman A Welch suggested that the matter might be one of public relations rather than economics. Dr Curlev moved the following amendment to the motion: "That the matter be referred to a joint meeting of the Committees on Medical Economics and Public Relations." The motion was seconded, and it was so voted. The President called for a vote on the motion as amended. It was so voted. Dr Bagnall said that all interested parties would be invited and set the time of the meeting as Wednesday, February 9, 1949.

A motion to adjourn was made and seconded, and it was so voted at 3 00 p m.

H QUIMBY GALLUPE, *Secretary*

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BRISTOL NORTH	A. P. George
J. V. Chatigny	H. R. Kurth
W. E. Dawson	R. C. Norris
J. L. Murphy	L. C. Peirce
W. M. Stobbs	F. W. Snow
BRISTOL SOUTH	C. T. Stokes
J. C. Corrigan	F. N. Sweetser
D. F. Gallery	C. A. Weiss
R. H. Goodwin	ESSEX SOUTH
William Mason	S. N. Gardner
C. C. Tripp	Loring Grimes
ESSEX NORTH	C. A. Herrick
M. F. Ames	P. P. Johnson
E. S. Bagnall	R. T. Moulton
	A. E. Parkhurst
	W. G. Phippen

E D Revnolds	G A Saunders	C II Bradford	Augustus Thorndike
H D Stebbins	E W Small	W J Brickley	Conrad Wesselhoeft
P E Tivnan	H P Stevens	W E Browne	
C F Twomey	K J Tillotson	A M Butler	
FRANKLIN	A B Toppan	A J A Campbell	WORCESTER
L R Dame	J B Townsend	E M Chapman	A W Atwood
J E Moran	J E Vance	M H Clifford	George Ballantyne
	C F Walcott	A P DerHagopian	F T Bousquet
	R H Wells	N W Faxon	Jacob Brem
HAMPDEN	Hovhannes Zovickian	Maurice Fremont-Smith	J B Butts
E P Bagg		Joseph Garland	J T B Carmody
R L Barrett	NORFOLK	G L Gately	F B Carr
G B Corcoran	C M Allard	A A Hornor	E J Crane
A J Douglas	B E Barton	C S Keefer	Paul Dufault
E C Dubois	Carl Bearse	H A Kelly	J J Dumphy
Adolph Franz, Jr	Elizabeth Brovles	T H Lanman	W J Elliott
J M Gilchrist	G L Doherty	C C Lund	John Fallon
Frederic Hagler	Albert Ehrenfried	C F Maraldi	Donald Hight
A G Rice	J M Faulkner	H L Musgrave	Thomas Hunter
G L Schadt	P S Foise	J P O'Hare	J A Lundy
J A Seaman	Susannah Friedman	L C Parkins	D K McCluskey
G L Steele	T R Goethals	L E Phaneuf	F A O'Toole
	H B Harris	Helen S Pittman	G L Richmond
MIDDLESEX EAST	C G Hayden	J H Pratt	N S Scarcello
J L Anderson	R J Heffernan	J J Regan	J J Tegelberg
T P Devlin	P J Jakmauh	W H Robey	R J Ward
Robert Dutton	I R Jankelson	Horatio Rogers	B C Wheeler
E M Halligan	L F Johnson	H F Root	WORCESTER NORTH
R W Layton	C J Kickham	C G Shedd	J J Curley
K L MacLachlan	C J E Kickham	R M Smith	J V McHugh
H L Mueller	D L Lionberger		C S McPeak
M J Quinn	D S Luce		J G Simmons
R R Stratton	C M Lydon		
J M Wilcox	D L Lynch		
	F P McCarthy		
MIDDLESEX NORTH	F J Moran		
R E Cole	H R. Morrison		
W E Collins	Hvman Morrison		
S A Dibbins	D J Mullane		
L J Hall	H A Novack		
J Y Rodger	W R Ohler		
A J Stewart	E E O'Neil		
J D Sweeney	R S Palmer		
	G W Papen		
MIDDLESEX SOUTH	H C Petterson		
E W Barron	H A Rice		
Harris Bass	D D Scannell		
J M Baty	J A Seth		
J D Bennett	L A Sieracki		
W O Blanchard	S L Skvirsky		
H K Bloom	E C Smith		
G F H Bowers	Kathleyne S Snow		
Madelaine R Brown	J W Spellman		
R N Brown	A R Stagg		
R W Buck	N A Welch		
J F Casey	G F Wilkins		
C W Clark	P R Withington		
E A Cooney	Marjorie Woodman		
W H Crosby			
J A Daley	NORFOLK SOUTH		
C L Derick	D L Belding		
J G Downing	Harry Braverman		
A G Engelbach	W R Helfrich		
W C Feeley	Frederick Hinchliffe		
J M Flynn	E K Jenkins		
H Q Gallupe	N R Pillsbury		
V A Getting	D B Reardon		
H G Giddings	H A Robinson		
H A. Godfrey			
A D Guthrie	PLYMOUTH		
Eliot Hubbard, Jr	J C Angley		
A M Jackson	G A Buckley		
F R Jouett	A L Duncombe		
H A Kontoff	Samuel Gale		
A A Levi	H H Hamilton		
A. N Makechnie	G A Moore		
J H McSweeney	SUFFOLK		
J C Merriam	H L Albright		
Dudley Merrill	A W Allen		
C E. Mongan	T J Anglem		
Fabyan Packard	M D Altschule		
L S Pilcher			

APPENDIX NO 2

REPORT OF THE EXECUTIVE COMMITTEE

A meeting of the Executive Committee was called to order at 1 00 p m on January 5, 1949, by the president, Dr Daniel B Reardon. The meeting followed a luncheon at the Harvard Club. All the officers of the Society were present. The councilors of Barnstable, Berkshire and Hampshire were absent.

The Secretary explained that the time of the meeting had been changed to allow for full discussion of all questions, that the Council might have the advantage of the discussions and with the hope that, as a result, the Council meetings might be shortened and improved. There were no matters referred to the Committee by the Council.

COMMITTEE REPORTS

Committee on Membership

The Committee met on December 8, 1948, and the Secretary submitted the report, which concerned requests for resignation with remission of dues, deprivation of membership for nonpayment of dues, deprivation of membership for nonpayment of district-society dues, and deprivation of membership for nonpayment and whereabouts unknown. This part of the report was accepted by the Executive Committee.

The discussion of additional categories of membership appears in Appendix No 3.

The Secretary was assured that the Executive Committee members had considered this matter as presented by the Committee on Membership very carefully. On motion duly made and seconded, the recommendation was unanimously approved.

NEW BUSINESS

The Secretary read a telegram from Dr George F Lull, secretary of the American Medical Association, received after the St. Louis Interim Session. "Recent Interim Session House of Delegates unanimously decided to assess each member of American Medical Association \$25.00. You are requested to collect this assessment through your county units or any other way you desire. Bill association for any extra expense in connection with the collection."

The Secretary pointed out that this assessment was permissible under the new by-laws of the American Medical Association, that the purposes of the fund were explained in an editorial in the *Journal of the American Medical Association*.

citation, issue of December 11, 1948, and that the fund was needed as soon as it could be collected. Dr John J Curley, a delegate, stated that it was a real emergency because the American Medical Association had no funds and that this was the first assessment ever made.

The Secretary then asked the committee to grant him permission to collect the assessment as an agent of the American Medical Association. Upon request, the Secretary quoted the following from the by-laws of the Society: "The Executive Committee shall authorize or confirm action by the officers in emergency."

Dr Arthur W Allen stated that if the committee agreed this to be an emergency, the Secretary could be authorized to act. Dr Donald Munro then moved that the committee declare that an emergency existed in relation to the collection of the assessment for the American Medical Association. The motion was seconded and unanimously carried.

Dr Munro then moved that the Executive Committee authorize the secretary of the Massachusetts Medical Society to act as an agent of the American Medical Association in the collection of the assessment. The motion was seconded by Dr Curley and unanimously voted.

REPORTS OF COMMITTEES IN CIRCULAR OF ADVANCE INFORMATION

Committee on Public Relations

The President called the attention of the committee to page 1, lines 22 to 25, of the report and said that he would leave it to the committee whether or not that should be acted upon. Dr Munro said the paragraph should be clarified. The Secretary said he had made the suggestion to the Public Relations Committee that they recommend that Dr Conlin be permitted to attend all meetings of all committees, that he might function better in his public-relations efforts. Dr Munro admitted the permission was justified, but doubted the propriety of a blanket permission to distribute information whenever Dr Conlin deemed necessary. Dr Allen suggested that Dr Munro rewrite the paragraph. Dr MacLachlan said he thought Dr Conlin ought to have the same privilege as the Secretary and the Treasurer — in other words, to attend meetings but without a vote.

Dr Conlin said he believed such permission would enhance the effectiveness of his position. Dr John Fallon said he believed the Society had employed Dr Conlin to acquire and dispense information according to his best judgment. Dr Reginald Fitz offered the suggestion that this recommendation might necessitate a change in the by-laws.

Dr Munro moved that paragraph 3 of the report on page 1 should be amended as follows: "It was the unanimous opinion of the committee that the Director of Medical Education and Information shall be a nonvoting member of all committees of the Massachusetts Medical Society. He shall be privileged to distribute the information acquired at such meetings after written approval of the committee or its chairman and further, it is the opinion of the Executive Committee that this action, if approved, be referred to the Committee on By-laws and Council Rules." The motion was seconded, and it was so voted.

The President then asked for a discussion of the paragraph beginning on line 45 of page 2 of the report. Dr MacLachlan said that he liked the code but thought it might not coincide with the code of the American Medical Association. Dr Conlin stated that the code was a forward-looking step in hospital-staff publicity problems. The press demanded to know Who What and When. Dr Stratton's committee was satisfied with the code as it stood. Dr Curley, Dr Munro and Dr Norman A Welch said that they had heard criticisms of the press release in *The Boston Herald* from the Massachusetts General Hospital of ten days ago. Dr Charles J E Kickham agreed. Dr Joseph L Murphy said that he believed the code was a proper step. Dr Curley moved that the code be referred back to the Committee on Ethics and Discipline for their further consideration and referred back to the Executive Committee. The motion was seconded, and it was so voted unanimously.

Committee on Legislation

The President drew the attention of the Executive Committee to lines 24 to 26 on page 4 of the report. "It was voted that the President of the Society appoint annually a Committee on National Legislation after consultation with the Committee on Legislation." Drs Fallon, Munro and

Curley considered this rather confusing, and Dr Belding said he believed the Committee on Legislation felt that it would be best to have a definite subcommittee so that work could be carried out harmoniously between the two, and that the President should have the power to appoint special men for special jobs at any time.

Dr Reginald Fitz suggested that the insertion of "sub-" before the word "committee" in line 25, page 4, would clarify the matter.

It was then voted to amend the report by the insertion of the prefix "sub-" before "committee" in line 25, page 4 of the report.

The Secretary then stated that he had asked the Committee on Legislation to make the recommendation beginning on line 32, page 4, so that the Society would have a method of co-operating with the Nurses Association in the writing of any proposed changes in the nurse-practice act. On motion duly made and seconded, the recommendation was unanimously approved.

Committee on Arrangements

This informational report was accepted.

Committee on Finance

Dr Buck presented the budget as printed and said that although some recommendations might be questioned, he believed all the increases could be justified.

Dr Lawrence R Dame wanted to know if there had been an increase in the use of the Library. Drs Fallon and Curley thought that there was an increase, but did not know to what extent. Dr Buck suggested that the Library might well make an annual report to the Society concerning the activities and accomplishments. Dr Curley, a trustee, said that he would bring that recommendation before them.

Dr Buck then brought up the recommendation beginning on line 37, page 6. The Secretary said that he had made that recommendation to the Committee on Finance after consultation with, and agreement from, Drs O'Hara and Bagg, who had made the salary arrangements originally. The Secretary pointed out the value of Dr Conlin's work and the danger to the Society if he was lost. Dr Reardon agreed. Dr Curley moved that the recommendation be approved. The motion was seconded, and it was so voted.

The Secretary stated that he had made the second recommendation to the Committee because of the value of Mr Boyd's work, and the inadequacy of his present salary because of the increased cost of living, and because Mr Boyd had three dependents. Dr Curley moved approval of the recommendation. The motion was seconded, and it was so voted.

Dr William M Collins moved that recommendation 3, line 47, page 6 be approved. The motion was seconded. Dr Reardon said that the Assistant Treasurer had not had a salary and that it was justified because of the increase in the work of tax returns, which he handled. The motion was carried unanimously.

Dr Lawrence Dame moved the approval of the fourth recommendation on line 50, page 6. The motion was seconded. The Secretary and Dr Conlin stated that a secretary to assist Dr Conlin was essential. He now had the part-time use of one of the three in the office. Dr Conlin stated that he believed this small investment would get a great deal more work out of the Director of Medical Education and Information. The motion was put to a vote and carried unanimously.

Dr Buck then called attention to recommendation 5, line 1, page 7, and said that it was confusing and was not a recommendation for a full-time secretary, but indicated an increase of \$2000 over what the committee spent in 1948 and was \$1500 more than the \$5000 budget for the year 1948. He said the increase was needed for all sorts of work of the committee, a good deal of which was secretarial in nature.

Dr Reardon then ruled that no action was necessary on this in particular and would be covered by approval of the budget as a whole. Dr Curley moved approval of the report as a whole. The motion was seconded, and it was so voted.

Committee on Industrial Health

The Executive Committee accepted the report as informational.

Advisory Committee on Malpractice Insurance

Dr Reardon introduced Dr Carl Bearer, who presented the report of his committee as printed. Dr Curley asked if

the Council had not already voted against the use of "listeners." The Secretary pointed out that the Executive Committee had opposed the use of "listeners," and that the Council had upheld the objection. Dr. Maclachlan said that there was not a large enough majority of insurance companies wanting the service to justify it.

Dr. Dame said that until a need was definitely made plain, he disapproved the use of listeners. Dr. George A. Moore said that he believed it a good idea and that it would have a salutary effect on many men who feel they say things in court with no objection being raised.

Dr. Maclachlan moved that the first recommendation be disapproved. The report was seconded, and it was so voted.

Dr. Curley said that the Executive Committee had previously refused to compile a list of experts for governmental agencies, and that it might not do so for insurance companies. Dr. Welch said that the recommendation suggested that whoever submits himself as an expert is *ipso facto* accepted as such. Dr. Curley moved that the second recommendation be disapproved. The motion was seconded, and it was so voted. Dr. Curley then moved approval of the third recommendation. The motion was seconded. Dr. Munro asked if this would not make the committee act over the head of the Committee on Ethics and Discipline. Dr. Curley suggested that insurance companies might report to this committee when they would not report to the Committee on Ethics and Discipline. On a show of hands, at the request of the President, the third recommendation was approved 8 to 5. The fourth recommendation was approved without discussion.

Dr. Arthur W. Allen and Dr. Dame then praised the committee for the good job it had done and hoped it would continue to keep in action. Dr. Maclachlan then moved that since the committee had done an outstanding piece of work, it should continue for further reports of progress. The motion was seconded, and it was so voted.

Committee on Emergency Medical Service

Dr. Fitz submitted the report as printed and stated that the committee had "leaned over backward" to present the Worcester plan as fairly as possible to the Executive Committee and the Council. The committee agreed that it should be as representative as possible, and chosen on as broad a base as possible. The Secretary said that usually a committee for a special project was better if small and appointed by the President after careful selection, and that this committee was just that. Dr. Allen thought that if the recommendation was approved the new committee might select an executive committee to carry the burden. Dr. Curley moved that the recommendation be disapproved. The motion was seconded.

The Secretary said that the committee now in existence and the present plan were formed at the suggestion of the Council on Emergency Medical Service of the American Medical Association and had the approval of the Council, and said that the committee would have to confer with the Governor's committee and might best be near Boston. Dr. Harvey A. Kelly suggested that a man from each district might be added to the present committee. The President put the question, and the motion was carried.

Dr. Curley then moved that the chairmen of the eighteen district committees as now constituted be added to the present committee. The motion was seconded, and it was so voted.

Committee to Meet with the Officers of the Bay State Rehabilitation Clinic

Dr. Charles H. Bradford submitted the report as printed and assured the committee that the clinic had the approval of the Commonwealth, that the doctors and laymen behind it were outstanding and that the orthopedic surgeons were behind it.

On a motion duly made and seconded, the first three recommendations were approved without further discussion.

Dr. Maclachlan moved the approval of the fourth recommendation after the President assured the committee that if the Council approved he would appoint the same committee. The motion was seconded, and it was so voted.

Advisory Subcommittee on Medical Education

This informational report was presented as printed, by Dr. Jankelson and accepted as such by the Executive Committee.

Committee on Diabetes

Dr. Howard F. Root presented the report as printed and asked permission to add a supplementary report. The Executive Committee gave its permission. (A mimeographed copy has been sent to each councilor with this report.) Dr. Fallon moved approval of the resolution, and the motion was seconded. There were several laudatory comments on the work of the committee, the benefits to the public and the fact that the whole program was a fine example of American medicine. The motion was carried unanimously.

Subcommittee on Blue Cross-Blue Shield Problems

Dr. Charles J. E. Kickham presented the report and stated that the first recommendation (line 27, page 26) was to make permanent the position held so successfully by Dr. McKittick during the past year. On motion duly made and seconded the recommendation was approved.

Dr. Kickham said that the second recommendation had originated with the Director of Blue Shield to get new blood into the fee committees. He also said that the third recommendation follows as a result of the second, and that the word "fee" should precede the word "committees" in line 35. On motion duly made and seconded these recommendations were approved. Dr. Kickham read the next recommendation, beginning on line 44, page 26. At the suggestion of Dr. Allen it was moved and seconded that the recommendation be approved and that lines 42 to 48 inclusive not be published in the proceedings. The motion was carried.

Dr. Kickham pointed to a typographic error on line 10, page 27 "dorian" should read "clarion." With this correction, the report was approved as a whole.

Committee on By-Laws and Council Rules

The report was submitted as printed with the correction of typographical errors on line 27, page 27 "by" and "rules" should be capitalized.

On motion duly made and seconded, the report was approved as a whole.

The President called for a motion to adjourn. The motion was made, seconded and so voted at 4:40 p.m.

H. QUIMBY GALLUPE, Secretary

APPENDIX NO 3

REPORT OF THE COMMITTEE ON MEMBERSHIP

The question was discussed whether there was any need for providing additional categories of membership in the Society to take care of physicians who might not be able to pay full membership dues. At a previous meeting in August, 1948, the Committee on Membership had been requested to make an investigation of this question and report their recommendations to the Executive Committee.

Four categories of physicians who might be unable to pay the full membership dues were discussed. First, medical students and hospital interns. It was believed that there was no particular advantage to these men in being full members of the Society and that the present arrangement, by which they were invited to attend all Society meetings and receive the *New England Journal of Medicine* by subscription, fully covered their needs.

Secondly, hospital residents. It was believed that very few of these men would be interested in full membership in the Society and if they were unable to pay the full dues they could apply for remission of dues on the grounds of financial hardship.

Thirdly, physicians on salaries from the Government and other agencies whose salaries are so low that payment of dues might be a hardship. It was believed that these physicians could be helped by applying for remission of dues on grounds of financial hardship.

Fourthly, physicians who are in their first year of practice and whose incomes might be limited. It was believed that these physicians definitely required the privileges of full membership in the Society and that the \$25.00 dues (amount-

ing to little more than \$2.00 a month) should be regarded by them as part of their investment in their medical careers and in fact, should be regarded as the most essential of their early medical expenses. It was believed that they could well afford \$2.00 a month in return for the valuable privileges that membership in the Society gives them and that there was no need for considering lowering membership dues for them.

Finally, the question of staggering dues from a lower level for young physicians to a higher level for older physicians, as is done by the Harvard Club, was discussed. It was believed that this would be an unwise practice since the dues of the Society represent payment for privileges received and are the same regardless of age or length of practice of the physician. The higher dues might cause more hardship to older physicians, whose incomes would be decreasing instead of increasing in later years of practice.

For these reasons, the Committee on Membership could see no need for any new categories of membership or change in the present schedule of dues. Any exceptional cases could be adequately handled under the current by-laws.

LEWIS S. PILCHER, *Chairman*
WILLIAM A. R. CHAPIN
PERCE H. LEAVITT
FRANCIS P. MCCARTHY
SAMUEL N. VOSE

APPENDIX NO. 4

REPORT OF THE COMMITTEE ON PUBLIC RELATIONS

The meeting of the Public Relations Committee of the Massachusetts Medical Society was held at the Harvard Club at 6:00 p.m., October 27, 1948. In addition to the representatives of eleven district societies there were present: President Daniel B. Reardon, chairman of the Committee, Dr. H. Quimby Gallupe, secretary of the Massachusetts Medical Society, Dr. John F. Conlin, director of medical education and information, and Mr. Robert St. B. Boyd, executive secretary.

The report of the Secretary, as printed in the advance notice of the meeting of the Council on October 6, 1948, was accepted.

Many of the representatives of the district societies reported the programs that had been initiated in their respective districts for emergency medical coverage. It was suggested that telephone companies could be of great help in securing physicians for emergency medical care, and that chambers of commerce were very willing to help in setting up emergency medical programs, more especially for daytime coverage.

It was unanimously voted that each representative notify the Secretary, Dr. Gallupe, of the particular plan for emergency medical coverage in effect in his District.

It was the unanimous opinion of the Committee that Dr. John F. Conlin, as director of medical education and information, should be privileged to attend all committee meetings he may desire and distribute the information as he shall deem necessary.

Dr. H. A. Robinson, Norfolk South, reported to the Committee his very favorable impressions of the work of the National Physicians Committee as a result of his recent attendance at a meeting of this organization. It was his opinion that there should be more effective co-operation with the National Physicians Committee through a more widely endorsed Massachusetts branch.

Dr. John F. Conlin discussed with the Committee the problem of the relation of the physician in matters of publicity, particularly with reference to the press and radio. It was his opinion that some sort of code should be established whereby physicians could govern themselves with reference to the release of information that might be considered of public interest. He, therefore, presented to the Committee a code that was recommended by the Executive Committee of the Eye and Ear Infirmary to the Board of Physicians in Ophthalmology and Otolaryngology for their consideration, because it was felt that such a code, if accepted by these two bodies, would further hospital publicity and afford a standard that would be welcomed by individual staff members faced with publicity problems. That code is as follows:

a The doctor's name may be used with the permission of the Chief of Service and the Infirmary's Assistant Director, to publicize the work of the Infirmary where the doctor is identified as a member of the staff rather than as an individual and where the accent is on the service and not on the individual doctor.

b The doctor's name may be used in connection with an individual case with the consent of the individual doctor as well as permission as above, where the case illustrates the work of the Infirmary and the accent is on the service to the patient and not on the doctor.

c The doctor's name may be used in information about a service or a patient, with permission as in a above, where the newspapers have most of the facts and are calling the Infirmary to verify data received through other sources.

d The doctor will supply information to the Public Relations Office on cases that are of interest to the newspapers, so that this office may issue accurate and beneficial bulletins.

e The doctor will feel free to supply data on cases that illustrate the services of the Infirmary provided the patient is willing to have his name used.

f The doctors on the staff may be relieved of calls from the press by stating that all Infirmary publicity is handled through the Public Relations Office. If, however, any contact is made by a doctor on the staff with the press or radio or a nonprofessional publication, the Public Relations Office requests that they be informed immediately.

This had been revised by the Committee on Ethics and Discipline of the Massachusetts Medical Society since the meeting of the Committee on Public Relations as follows:

(Revised) The doctors on the staff should refer all calls that come to them from the press and that deal with Infirmary publicity, to the Public Relations Office, to be cleared as in a above. If any contact is made by a doctor on the staff with the press or radio or nonprofessional publication, the Public Relations Office should be informed immediately.

g The staff will keep in mind the needs of sound hospital publicity and will make suggestions to the Public Relations Office about cases or services that could be publicized.

h A staff member will be willing to be interviewed by name on a phase of the Infirmary's work if the Chief of Service approves and, if it is a newspaper interview, if the reporter is willing to submit proof before publication.

It was the unanimous opinion of the Public Relations Committee that this code, which could serve as a standard by physicians in matters of publicity, should be referred to the Committee on Ethics and Discipline for their approval.

Dr. John F. Conlin further informed the Public Relations Committee of the various activities of his office:

a He served as Chairman of the local Publicity Committee at the American Public Health Association Meeting in Boston recently.

b At the National Public Relations Conference, which is to be held at St. Louis just prior to the interim session of the House of Delegates of the American Medical Association (November 30-December 3, 1948), Dr. Conlin will address the Annual Conference of Secretaries and Editors of State Medical Associations on the use of radio in medical society Public Relations programs.

c Requests for information and for speakers on "Socialized Medicine" are increasing. There is thus urgent need for study and dissemination of information concerning basic economic factors affecting medical practice.

d Favorable progress is being made with reference to the Health Conference sponsored by the Society. An Executive Committee has been formed and will meet to organize. It is planned to bring together a large group of "consumers" and "distributors" of medical care for a two-day meeting in Boston next February.

e Attention was again called to the fact that, of the 9100 physicians in Massachusetts, only 6600 are fellows of the Society. It is felt that there is urgent need for the extension of the Gallupe Plan in various hospitals and for the intensification of efforts to make educational facilities

available to physicians desiring to qualify for membership in the Massachusetts Medical Society

f Progress continues in the field of inter-professional relationship Drs Reardon and Conlin were recently speakers at a meeting of the Metropolitan District Dental Society

g The current status of the Anti-vivisection and Pound Law legislation was briefly reported A special committee to study the use of animals for medical experimentation has been appointed by the general court and the governor This commission, of which Dr Conlin is one of the eleven members, is expected to report its findings in December, 1948

h With reference to the matter of the Health Exhibit to be sponsored by the Massachusetts Medical Society in the fall of 1949, a committee is expected to function in the immediate future with reference to this project

i Visitations by the officers of the State Society to the various Districts are reported to be of distinct benefit and should be encouraged

j There is a definite falling off in the number of complaints received concerning night calls and lack of availability of physicians for emergency medical coverage However, there still remains much to be done by the District Societies with reference to this important matter

k The press and radio in Massachusetts have generally been favorable to the cause of high standards of medical practice and to the promotion of public health A cross-filing system has been found to be very helpful in the assembling of news coverage and editorial attitudes of most publications There has been a distinct increase in the activities of the District Societies to assist the State Society in its work Also, voluntary agencies and public officials, working in the field of health, have shown an excellent willingness to co-operate with the Society in its various endeavors and programs

The meeting adjourned at 10 00 p m

HAROLD R KURTH, *Secretary*

APPENDIX NO 5

REPORT OF THE COMMITTEE ON LEGISLATION

An informal meeting was held on May 24 without organization of the committee for the 1949 session It was voted, however, that S L Skvirsky, councilor from Norfolk, act as chairman until a permanent chairman could be elected

At the meeting held on October 6, 1948, the general policies, procedures and activities of the committee were discussed and formulated Special powers were again delegated to an executive committee of five, to be appointed by the chairman of the committee Mr Charles J Dunn was again named legislative counsel The 1949 budget was discussed and action was postponed until the next meeting

At the November 17 meeting the following officers were elected chairman, Solomon L Skvirsky, Norfolk, secretary, David L Belding, Norfolk South, and assistant secretary, Alfred L Duncombe, Plymouth

The 1949 budget was considered, and in view of the greater activity in national legislation it was voted to submit a budget for \$6500 to the Committee on Finance After considerable discussion regarding the status of the Committee on National Legislation, it was voted that the president of the Society appoint annually a committee on national legislation after consultation with the Committee on Legislation, that all reports and actions of the subcommittee be cleared through the legislative committee, and that the president make such additional emergency and temporary appointments for handling national legislation as in his opinion the situation demands The matter of probable new legislation regarding the registration of nurses came to the attention of the Committee It was voted that the Committee recommend to the Council that the president appoint a committee of five to meet with the Massachusetts Nursing Association

The 1949 Massachusetts legislative session will begin on January 5, 1949, and in all probability new committees in both branches of the General Court will be named at this time It is hoped that the printed bills will be available also

The role of the federal Government in the development and financing of social programs in the fields of health and social welfare generally is a factor of major importance

The Eightieth Congress enacted several new health laws They voted increased appropriations to expand many of the existing federal and state health and social welfare programs Neither the Taft Bill (S 545) nor the Wagner-Murray-Dingell Bill (S 1320) was acted upon because it was decided that further study was necessary This respite was made possible by the adoption of Senate Resolution 249—introduced by Senator H Alexander Smith, of New Jersey The resolution provided for the use of the Subcommittee on Health \$10,000 to continue its study of national health problems

The Hoover bipartisan commission established to study and prepare plans for reorganization of the federal Government will submit its recommendations to Congress early in January Action on the favorably reported bill to create a department of health, education and security under a head with cabinet rank was postponed until the Hoover Commission makes its report

The officers and the following legislative councilors will constitute the executive subcommittee on legislation William E Browne, Suffolk, Arthur H Riordan, Hampden, and John B Butts Worcester

SOLOMON L SKVIRSKY, *Chairman*

APPENDIX NO 6

REPORT OF THE COMMITTEE ON ARRANGEMENTS

A meeting of the Committee on Arrangements was held at 8 Fenway, November 10, 1948 Besides the members of the Committee and officers of the various scientific sections of the Society, the meeting was attended by President Dr Daniel B Reardon, President-Elect, Dr Arthur W Allen, Dr W Richard Ohler, of the Committee on Postgraduate Education, Dr George R Dunlop, of Worcester, and Mr Robert St B Boyd

Attention was called to the fact that the first committee on arrangements had been appointed February 20, 1849, and that the present committee is, therefore, the one hundredth consecutive such group to serve the Society The only older committee is that on publications, which was established in 1825 and which has functioned since then without interruption

The 1949 annual meeting will be held at the Memorial Auditorium in Worcester, May 24, 25 and 26 It is interesting to note that the first meeting of the Society held outside Boston was in that city—in May, 1851 Since then the Society has been the guest of the Worcester District three times in 1928, 1934 and 1939

The formation of a three-day scientific program, which shall include at least some subjects acceptable to all members of the Society, avoiding matters that are too technical and covering for the most part problems with which the general practitioner has to deal, is not an easy matter It requires careful, thoughtful and unhurried study, involving, as it does, the selection of speakers as well as of subjects

In approaching the problem this year, the Committee has followed the recent custom of inviting the officers of the several sections to sit in with us and to give us suggestions toward the attainment of such a program Their contributions have been very helpful and will form the basis of the final program

The Committee has also received requests regarding subject matter for the program from practicing members in various parts of the Commonwealth and so far as practicable their requests will be included

The Worcester District Society, through a committee headed by Dr George Dunlop, is working in close co-operation with the Committee and through them it is hoped that a goodly representation of speakers from the central and western parts of Massachusetts will consent to give papers and that the hospitals in those sections will favor us with interesting exhibits In response to several requests present plans call for more movies because of their educational value than have recently been shown

The newly formed Woman's Auxiliary of the Massachusetts Medical Society will be responsible for entertaining the ladies, with Mrs Charles Ayers, of Worcester, the vice-president, as chairman As usual, the countless details of

organizing the mechanics of the convention are under the efficient direction of Mr Robert St B Boyd executive secretary of the Society. For his interest and tireless effort the Society is greatly indebted.

HAROLD G GIDDINGS *Chairman*
FRANKLIN G BALCH, JR
GORDON DONALDSON
ALBERT EHRENFRIED
JOHN W NORCROSS

APPENDIX NO 7

REPORT OF THE COMMITTEE ON FINANCE

The Committee on Finance presents its report of the expenditures of the Society during 1948. Figures for November and December are estimated, so that the total amounts are only approximate, but reasonably accurate. The budget for 1949, agreed upon by the Committee at a meeting held November 23, 1948, is also presented.

The 1949 budget exceeds that for 1948 by nearly \$56,000, representing added expenditures of more than \$10 for each member of the Society and amounting to an increase of about 65 per cent over last year. This rise is accounted for largely by the cost of membership in the Boston Medical Library (\$27,000), the contribution to the Medical Benevolent Society (\$10,000) and increases in salaries (\$11,000), all of which were authorized by vote of the Council or requested by officers of the Society or have appeared in committee budgets.

Your approval of these salary rises is invited in the following recommendations by the Committee (all of which are included in the budget).

An increase of \$1500 in the salary of the Director of Medical Information and Education above that provided in your action last year by which annual increases were to amount to \$500 each year until a total salary of \$10,000 was reached. It is the opinion of the officers of the Society, the members of the original committee that chose the Director and of other representative fellows that the full salary should be paid beginning in 1949 instead of in 1952.

An increase of \$1200 in the salary of the Executive Secretary requested by the officers of the Society and approved by the Committee.

Provision of a salary of \$500 for the Assistant Treasurer, whose duties have increased under the present situation requiring the preparation of tax returns.

Provision of secretarial service for the Director of Medical Information and Education at a cost of \$2000.

Provision of secretarial service for the Committee on Legislation, which would add \$2000 to the sum otherwise allotted this committee.

It is only proper that the attention of the Society be called to the fact that our expenses are closely approaching our estimated income in amount. If we are able to live within our budget during 1949, there will be a surplus of only \$8000 to be turned into the Building Fund. If our expenses continue to rise, provision for a larger income, presumably by a further increase in the annual dues, will have to be considered. This is desired by no one. The alternative is a conscious effort on the part of all concerned to reduce expenses wherever possible.

ROBERT W BUCK, *Chairman*
FRANCIS C HALL
FABYAN PACKARD
BANCROFT C WHEELER
CHARLES F WILINSKY

DETAILED EXPENDITURES — 1948

Salaries

Secretary (up to July \$3,500 since July \$5,000)	\$8,500 00
Executive Secretary	4,800 00
Treasurer	2,000 00
Assistant Treasurer	500 00
Director of Medical Information and Education	8,000 00

Expenses of Officers

President

Harvard Club	\$26 12
Personal	163 54
Travel	48 03

Estimate for November and December

237 74
138 00

375 74

375 74

President Elect

Harvard Club	4 95
Estimate for November and December	74 00

78 95

78 95

Secretaries

Printing	1,703 92
Travel	264 04
Reporting meetings	314 10
Supplies	295 98
Telegrams	25 28
Washington Report	39 40
Binding	71 75
Meals	2 62
Petty cash	5 50
Tuition of office secretary	42 50

2,763 09

625 09

Estimate for November and December

3,393 09

3,393 09

Treasurer

Premium on bond	37 50
Public accountant	315 00
Rent deposit box	18 00
Petty cash	27 65
Loomis-Sayles Company	1,266 62
Printing and envelopes	237 44

1,902 21

176 00

Estimate for November and December

2,078 21

2,078 21

Director of Medical Education and Information

Newspaper	231 40
Equipment	681 43
General expenses through May	1,083 76
Mailing and addressing	526 84
Telegrams	143 21
Travel	184 68
Petty cash	91 64

2,748 01

1,700 00

Estimate for November and December

4,448 01

Credit incorrect charge belonging to Pound Law account

300 00

4,148 01

4,148 01

Delegates to A M A

Shattuck Lecture

Deduct Income Shattuck Fund	185 34
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16 66

16 66

Cotting Lurchsons

Deduct Income Cotting Fund	450 00
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160 00

290 00

290 00

General Administration

Servicing and supplies for machines	407 20
Envelopes, paper, stamps, office equipment	2,522 34
Telephones	592 99
Printing and binding	259 80
Addressing	25 00
Petty cash	478 38
Mailing	77 29
Insurance	58 14
Washington Report	15 00
Microphones, cabinets, etc.	214 75
Premiums on Blue Cross	144 00
Travel — Mr Boyd and Dr Garland	561 66
Meal with real estate agent	3 95

4,940 50

907 00

Estimate for November and December

5,847 50

194 81

Credit Addressing, Service District Societies

5,652 69

6,240 00

Massachusetts Medical Society Clerical

11,597 69

11,592 69

Committees

Executive

Meals	35 05
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33 05

Legislation

Charles Dunn	3,500 00
Telegrams	143 98
Mailing	32 09
Meals	395 04
Secretarial expenses	29 86
Legislative Reporting Service	231 88
Subscription Washington Report	45 00
Travel — Dr Bagnall	83 92

4,461 77

Estimate for November and December	58 00			Special Committees			
Credit on Parker House bill	4,519 77			Information Bureau			
	8 00			Wages	2,184 00		
	4 511 77	4 511 77		Supplies	161 42		
Public Relations				Stamps	176 00		
Meals	187 77			Extra secretarial	61 93		
To Massachusetts State Nurses Association	50 00				2,583 35		
	237 77			Estimate for November and December	176 71		
Estimate for November and December	298 00			Credits	2 760 06		
	535 77	535 77			5 04		
Arrangements					2 755 02	2,755 02	
Tickets and printing	655 00			Cancer	—		
Badges	162 87			Fee Schedule	—		
Envelopes and supplies	780 20			Malpractice Insurance	—		
Petty cash	38 81			Medical Economics	—		
Refunds on booths	330 00			National Emergency Service			
Vassar scholarship	62 50			Printing and postals	176 50		
Proofreading	4 50			Dr. Gallupe to Chicago	37 05		
Prizes	45 70				213 55	213 55	
Travel expenses — speakers	572 95						
Mailing	111 10			New England Postgraduate Assembly			
Refunds on tickets	21 00			Envelopes and supplies	745 90		
Entertainment — ladies	588 00			Printing	367 19		
Ladies Committee expenses	374 02			Advertising	128 00		
Publicity	92 36			Addressing	108 02		
Golf Tournament	15 00			Refund	2 50		
Statler bill	9 253 76			Cash for registration desk	100 00		
Quarter rental hall — Worcester	250 00				1 451 61		
	13 357 77			Estimate for November and December	3 901 00		
Estimate for November and December	46 00				5 352 61		
	13 403 77			Income	6 502 50		
Income	16 677 95			Expense	5 352 61		
Expense	13 403 77			Profit	1 149 89		
Profit	3 274 18			Postgraduate Education			
Ethics and Discipline				Printing	350 73		
Meals	53 39			Lectures	2 234 79		
Petty cash	40			Envelopes addressing and mailing	266 41		
	53 79			Meals	171 89		
Estimate for November and December	10 00			Janitor Sanders Theater	80 00		
Credit overpayment	63 79			Expenses Sanders Theater	371 71		
	47				3 475 53		
	63 32			Estimate for November and December	155 00		
Deduct Income Brickley Fund	20 00				3 630 53		
	43 32	43 32		Credit — Commonwealth of Massachusetts	575 00		
Finance	—				3 055 53	3 055 53	
Industrial Health	41 83	41 83		School Medical Services	—		
Medical Defense				Special Services	—		
Palmer Dodge Chase & Davis	2 244 37			Expert Testimony			
Estimate for November and December	628 00			Meals	88 83	88 83	
	2 872 37	2 872 37		Tax Supported Medical Care			
Membership				Meals	36 31	36 31	
Estimate for November and December	41 00			Other Expenditures			
	41 00	41 00		Refund to district societies		8 000 00	
Publications				Dues Council N E State Medical Societies		100 00	
Meals	38 21			To carry New England Journal of Medicine		5 000 00	
Estimate for November and December	28 00			Premium Pension Plan	4 233 80		
	66 21	66 21		Less dividend	153 40		
Public Health					4 080 40	4 080 40	
Massachusetts Central Health dues	10 00			Pound Law Account			
Meals	31 25			Mailing and postage	348 07		
	41 25			Advertising	1 967 60		
Estimate for November and December	40 00			Letters and envelopes	275 00		
	81 25	81 25			2 590 67		
Society Headquarters				Income received in gifts	2,800 00		
Electricity	227 86			Refund on advertising	7 56		
Cleaning	215 50				2,807 56		
Rent	2 437 48			Profit	216 89		
Painting	695 00			To Friends of Medical Progress	216 89		
Electrical installations	307 00				000 00		
Carpentry	64 00			Taxes — 1948			
	3 946 84			Federal Old Age Tax	171 00		
Estimate for November and December	946 00			Estimate 4th Quarter	34 00		
	4,892 84				205 00		
Credits	69 16			State Unemployment Tax	461 66		
	4 823 68	4 823 68		Estimate 4th Quarter	90 00		
					551 66		

Federal Unemployment Tax

Paid at year end 0.3% of all wages less deductions. Estimate

62 00

Prior Taxes paid in 1948
(will not recur annually)

1 State Unemployment Tax for last quarter 1944 and all of 1945 1946 1947

1 060 05

2. Interest charge on same

100 58

3 Additional tax on 1947 for unlawfully claiming deduction on Pension Plan Premium

114 31

1 274 94

Prior State Unemployment Tax on Journal for last quarter of 1944 through all of 1947 Amount assumed by Massachusetts Medical Society (one half total of \$2,179.91) by vote of Council

1 059 96

2,364 90

Amount Paid to Boston Medical Library

25 660 00

Estimate for November and December

1 180 00

26 840 00

2 364 90

26,840 00

Profit and Loss Account

General Fund Loss

893 34

General Fund Profit

31 25

Net Loss

867 09

867 09

\$115 00 64

INCOME, 1948

Censor Fees

\$495 00

Estimate for November and December

738 00

Sale of Directories

Annual Dues

1 233 00

164 00

Estimate for November and December

129 583 00

6,200 00

Less refunds

135 788 00

143 00

Nonresident Dues

Estimate for November and December

135 645 00

2 003 00

12 00

Income General Fund

Estimate for November and December

2 520 00

5 305 49

1 211 00

Profit Committee on Arrangements

Profit Postgraduate Assembly

6,516 49

3 274 18

1 149 89

\$10,502.56

REPORT OF COMMITTEE ON FINANCE — BUDGET FOR 1949

BUDGET 1948	EXPENDITURES 1948		BUDGET 1949	CHANGE	
		SALARIES			
\$6 600 00	\$8 300 00*	Secretary	\$10 000 00	+	\$3 400 00
4 800 00	4 800 00	Executive Secretary	6 000 00	+	1 200 00
2,500 00	2,500 00	Treasurer	2,500 00	—	—
—	—	Assistant Treasurer	500 00	+	500 00
8 000 00	8 000 00	Director Medical Information and Education	10 000 00†	+	2,000 00
EXPENSES OF OFFICERS ETC.					
300 00	375 74	President	300 00	—	—
100 00	78 95	President-Elect	100 00	—	—
3,500 00	3 393 09	Secretary	3,500 00	—	—
2,000 00	2 078 21	Treasurer	2,000 00	—	—
(2,900 00)	4,148 01	Director Medical Information and Education	6 060 00‡	+	3 160 00
1 600 00	1 886 75	Delegates to A.M.A.	2,500 00	+	900 00
200 00	16 66½	Shattuck Lecture	200 00‡	—	180 00
350 00	250 00	Cotting Luncheons	300 00	—	50 00
9 100 00	11 592 69	General Administrative Expense	12,000 00	+	2 900 00
COMMITTEES ELECTED BY DISTRICT SOCIETIES					
400 00	33 05	Executive	200 00	—	200 00
5 000 00	4,511 77	Legislation	6,500 00	+	1,500 00
600 00	535 77	Public Relations	600 00	—	—
STANDING COMMITTEES					
200 00	Profit	Arrangements (Income over expense \$3 274 18)	200 00	—	—
50 00	43 52	Ethics and Discipline	50 00	—	—
25 00	—	Finance	25 00	—	—
400 00	41 83	Industrial Health	150 00	—	250 00
1,500 00	2,872 37	Medical Defense	2,000 00	+	500 00
150 00	41 00	Membership	150 00	—	—
200 00	66 21	Publications	75 00	—	125 00
10 000 00	5 000 00	To carry <i>New England Journal of Medicine</i>	10 000 00	—	—
—	—	Publication of new Directory of Fellows	3 000 00	+	3 000 00
250 00	81 25	Public Health	200 00	—	50 00
4,100 00	4,823 68	Society Headquarters	4,100 00	—	—
SPECIAL COMMITTEES					
3,500 00	2 755 02	Bureau of Clinical Information	3 000 00	—	500 00
50 00	—	Cancer	50 00	—	—
—	—	Council Rules and By-laws	350 00	+	850 00
—	88 83	Expert Testimony	—	—	—
50 00	—	Fee Schedule	—	—	50 00
200 00	—	Malpractice Insurance	200 00	—	—
75 00	—	Medical Economics	75 00	—	—
—	213 55	National Emergency Service	200 00	+	200 00
1 000 00	Profit	New England Postgraduate Assembly (Income over expense \$1 149 89)	1 000 00	—	—
3,500 00	3 055 53	Postgraduate Education	3,500 00	—	—
75 00	—	School Medical Services	—	—	75 00
500 00	—	Special Services	—	—	500 00
—	36 31	Tax Supported Medical Care	50 00	+	50 00
OTHER EXPENDITURES					
8 000 00	8 000 00	Refund to District Medical Societies	8 000 00	—	—
100 00	100 00	Dues, Council New England State Medical Societies	100 00	—	—
4 014 00	4 050 40	Premium, Pension Plan	4,100 00	+	86 00
—	—	Medical Benevolent Society	10 000 00	+	10 000 00
—	26,840 00	Boston Medical Library	27 000 00	+	27 000 00
670 00	—	Taxes	1 000 00	+	350 00
—	205 00	Federal Old Age	—	—	—
—	551 66	State Unemployment	—	—	—
—	62 00	Federal Unemployment	—	—	—

REPORT OF COMMITTEE ON FINANCE — BUDGET FOR 1949 (Concluded)

PRIOR TAXES			
1,060 05	State Unemployment Tax 1944-1947		
100 58	Interest		
114 31	Additional tax on 1947 for unlawfully claiming deduction on Pension Plan Premium		
1 089 96	State Unemployment Tax on <i>Journal</i> 1944-1947, one half of total amount (\$2 179 91) assumed by Massachusetts Medical Society by vote of Council		
867 09	General Fund Loss on sale of securities		
<u>\$86 359 00</u>		<u>\$115,030 64</u>	
			<u>\$142 155 00</u>
			<u>+ \$55 796 00</u>

*January-July \$3,300 00 July-December \$5 000 00 (by vote of Council)

†Subject to vote of Council.

‡Includes \$2 000 00 for secretary to Director

§Reduction due to income from Shattuck Fund.

INCOME DURING 1948

(Actual figures available for first ten months of the year, figures for November and December are approximate but included in total)

Annual dues	\$135,645 00
Nonresident dues	2,520 00
Censor fees	1 233 00
Sale of directories	164 00
Income, General Fund	6 516 49
Profit Committee on Arrangements	3,274 18
Profit, Postgraduate Assembly	1 149 89
	<u>\$150 502 56</u>

APPENDIX NO 8

REPORT OF THE COMMITTEE ON INDUSTRIAL HEALTH

This report is informational only. The Committee on Industrial Health is alert to the proposed development of a health service for federal employees in Boston in the near future and its probable later extension to the larger communities within the Commonwealth. In this regard your committee chairman has had several conferences with representatives of the United States Public Health Service and this committee, with Dr J J Poutas representing the Committee on Public Health and Dr John F Conlin, director of medical education and information, held a formal meeting with Dr Murphy and Dr Weiskopf, of the Public Health Service, to be informed upon the workings of the proposed health service. Dr Murphy had recently completed a survey for the organization of the health service in Boston and was preparing recommendations for its establishment, and Dr Weiskopf reported upon the operation of the service, which he directs in the United States Treasury Dept., Washington, D C.

The Health Service for Federal Employees came into being as the result of Public Law 658 favorably passed upon by the Seventy-Ninth Congress on August 8, 1946. Thus far units have been established only in Washington, D C, St Louis and New Orleans. The actual establishment and operation of a unit depends upon appropriation of the necessary funds by Congress. So far no appropriation has been made for the proposed unit in Boston, but we are advised by letter of December 10 from the medical director of the Division of Federal Employee Health, United States Public Health Service, that a recommendation for such funds is now in preparation and is to be acted upon by the next Congress.

The law emphasizes the prevention of illness but does not provide for general medical care. Specifically it provides for

- Treatment of on-the-job illness and dental conditions requiring emergency attention
- Pre-employment and other health examinations
- Referral of employees to private physicians and dentist.
- Preventive programs relating to health

It is proposed to establish a main unit in the Federal Building in Post-Office Square, staffed by qualified personnel, physicians, nurses, technicians and others associated with or supervised by the Public Health Service, adequately equipped with x-ray and other diagnostic aids and to establish six so-called satellite units in other federal agencies in Boston proper. In his recent letter the medical director of this service states "We are quite cognizant with the fact that competent and qualified professional personnel today demand and properly should receive remuneration commensurate with the duties required of them."

With the approval of Dr Reardon, president of the Massachusetts Medical Society, the Committee on Industrial Health and the representatives of the United States Public Health

Service have mutually agreed to co-operate in the development of this health service for federal employees in Boston and in the Commonwealth of Massachusetts to the end that it shall be ethical, that it will be consistent with the high ideals of industrial medicine as interpreted by the American Medical Association and the Committee, and that it will in no way conflict with the privileges of the private physician or his patient relationship but will, rather, enhance them. So far the representatives of the United States Public Health Service have been most co-operative.

DANIEL L LYNCH, *Chairman*
JOSEPH C AUB
LOUIS R DANIELS
JOHN G DOWING
HAROLD R KURTH
FRED N MANLEY
HENRY C MARBLE

APPENDIX NO 9

REPORT OF THE ADVISORY SUBCOMMITTEE ON MALPRACTICE INSURANCE

Since our previous report to the Council letters were sent to 22 insurance companies — all the companies we had reason to believe might write malpractice insurance in Massachusetts. In these letters the insurance companies were informed of the existence of this Committee and of its desire to co-operate with them. Inquiries were also made as to

Whether the Committee could help in the selection of experts to testify at trials for malpractice.

Whether insurance companies would like to have the Committee review physicians' medical testimony that may seem to be below the standard applicable to members of the Massachusetts Medical Society.

Whether "listeners" at trials were advisable and how often this might be necessary (Suggested by an insurance company).

The number of suits currently pending against members of the Massachusetts Medical Society, the number of new suits filed during 1947, and the number terminated that year.

Replies were received from all companies. 5 stated they were not writing malpractice insurance in Massachusetts. Practically all the companies writing this type of insurance, and several who do not, commended the idea of the establishment of this committee and expressed their desire to co-operate.

Eleven companies were very definite that the Committee could help in the selection of experts, one company hedged a bit, and 10 made no comment.

Eight companies stated they would be glad to avail themselves of the services of this committee. The remaining companies made no comment.

Fifteen companies replied to the question regarding "listeners", 11 companies unreservedly approved the idea, 1

company qualified its approval, 1 company questioned the value of "listeners", 2 companies said it "would seem to have some merit, but it is something which should be given further study", 7 companies made no comment.

All the companies writing malpractice insurance replied to the question regarding the number of suits. Sixty-four new suits were entered during 1947, 45 suits were terminated that year either by settlement or verdict. A total of 147 suits were pending.

To this total of 147 suits should be added 9 suits being handled by the Committee on Medical Defense of the Society, or a grand total of 156 suits outstanding.

These figures, of course, may change from day to day, but do give a good idea of the current malpractice situation as it affects the members of the Society. It is possible that some claims were settled before any suit was filed, but it is unlikely that insurance companies would pay any substantial amount unless a suit were entered in court.

At a meeting of the Committee on December 1, 1948, in view of the replies received, it was voted that the following recommendations be made to the Council:

That the Committee compile a list of "listeners" — these names to be obtained by a letter to all the district societies to be read at their meetings, asking that men desiring to be "listeners" communicate with the chairman of this committee.

On request for a "listener" by an insurance company, the company would be furnished with a list of appropriate names and the company would make its own selection and arrangements. This would mean that the "listener" would not be present as representing the Society but as being retained by the insurance company. If he appeared as "listener" for the Massachusetts Medical Society, no gratuity would be paid, this would be considered a service to the Society.

That the Committee compile a list of experts. The district societies would be asked to submit names of men who are willing to testify and their specialty. This list would be submitted to insurance companies on request. The companies would make their own selection and arrangements.

That the Committee review the testimony of members reported as being below the standard expected of members of the Society. If testimony is substandard, this fact would be reported to the Committee on Ethics and Discipline.

That insurance companies be informed of the recommendations approved by the Council.

CARL BEARSE, *Chairman*
WILLIAM J. BRICKLEY
MAURICE FREMONT-SMITH
HORATIO ROGERS
CHARLES D. MCCANN

APPENDIX NO 10

REPORT OF THE COMMITTEE ON EMERGENCY MEDICAL SERVICE

The exact part to be played by the Massachusetts Medical Society in relation to emergency medical service for the nation is at present uncertain. One fact, however, is clear: arrangements must be made so that doctors in different parts of the Commonwealth are organized to render emergency service in case of need and according to a well thought out plan.

The present committee was appointed by the Council in June. Shortly after its appointment, Dr. N. S. Scarcello introduced to the Council, as new business, a statement from the Worcester District Medical Society, which was referred to the Committee for study.

Briefly put, the Worcester District Medical Society objects to the appointment of members of an emergency medical service committee by the Council, believing that so important a committee should be more representative and should be elected by the district societies.

From the viewpoint of operability, the Worcester District Medical Society appears to have in mind reconstruction of the Procurement and Assignment Service of World War II in its essential details. As will be recalled, during those hectic days each district society had its own procurement and assignment committee with chairman and members appointed in such fashion as the district society desired. The function of such local committees was to keep track of medical needs within their territory, determining which of its physicians could be declared available for military

service, which were essential for civilian needs, and what procedures should be adopted to meet any local medical catastrophes that might arise.

After the Procurement and Assignment Service was established by the War Manpower Commission in Washington, its chairman was appointed by the Commission, his task was to obtain information from local committees and to keep track of what was going on at the state level. This he did with the assistance of a committee appointed for the purpose by the Council.

The Worcester District Medical Society believes that a more effective operation of this general plan would result if the chairman of each local committee served on the committee of the Society and if the committee elected its chairman instead of having its chairman appointed by the Council or by an outside agency.

The present committee finds no objection to such a procedure. Therefore, the committee makes two recommendations:

The Committee on Emergency Medical Service shall be appointed by the Council. It shall consist of one representative from each district society, to be chosen in such fashion as each district society may determine, provided that he shall be chairman of the Committee on Emergency Medical Service of his district society and a member of the Council. The chairman of the committee shall be elected from its members on call by the President.

If this recommendation is adopted by the Council, the present committee recommends that it be discharged.

REGINALD FITZ, *Chairman*
CHARLES H. BRADFORD
EDWARD D. CHURCHILL
DONALD E. CURRIER
EUGENE C. EPPINGER
J. ROSWELL GALLAGHER
ALLEN JOHNSON
THOMAS H. LAMMAN

APPENDIX NO 11

REPORT OF THE COMMITTEE TO MEET WITH THE OFFICERS OF THE BAY STATE MEDICAL REHABILITATION CLINIC

The Committee to confer with the Bay State Medical Rehabilitation Clinic met on December 8, 1948, and studied the plans already proposed for putting the Clinic into operation. Representing the Committee, the following members were present: Drs. Reardon, Gallupe, Barr, Hermann, Clark, Bauer, Bradford and Watkins, and representing the Clinic were Dr. Augustus Thorndike and the nonmedical members George Batchelder, Henry White and Charles Hodges. A program already prepared to describe the work of the Clinic was read. It will be referred to in the report as "The program." As a result of this conference, the Committee has the following report to submit:

It has been clearly shown that a substantial number of industrial and nonindustrial accidents, as well as disabling diseases, lead to partial or permanent disability every year. These accidents and diseases cause a heavy burden of loss to the persons who suffer from them, and also the community as a whole is seriously handicapped. Immediate treatment for injuries or sicknesses is available to all through hospital centers and public and private care, but there is a great lack of co-ordinated systems of rehabilitation to carry the patient through convalescence and back to the point where a normal occupation can be resumed. To meet this lack, the Bay State Rehabilitation Clinic has made plans for the organization of a center where the services of medical and surgical consultants and physical and occupational therapists will be combined with social-service aid and with vocational-guidance counselors. By co-ordinating these related services toward the one comprehensive purpose of rehabilitation, this clinic will carry out its plan more completely and on a larger scale than could be done by any individual or private agency. It will help private physicians who may wish to refer to its services any cases under their care, and it will supplement any existing industrial or hospital clinics that may call upon its aid for rehabilitation. The directorate of this clinic is made up of men of outstanding ability, and their program has been studied with

great care. There is no doubt that the work of such a group as this is urgently needed and will be well carried out. The Committee therefore recommends

That the Massachusetts Medical Society support the Bay State Rehabilitation Clinic with a complete endorsement of its program, and offer full co-operation in helping to carry out its important aims

That the first clinic should be inaugurated in Boston, to serve eastern Massachusetts, because of the availability of consultants here and the heavy concentration of industrial groups within commuting distance

That the progress and success of this clinic be used as a guide for opening other clinics in the western part of the Commonwealth as soon as this course should seem practical

That, having discharged its purpose by rendering this report, the present committee be discontinued and replaced by a working committee to be appointed by the President for the purpose of observing the Bay State Rehabilitation Clinic and consulting with its directors and assisting and making recommendations wherever they may prove helpful as new problems are encountered

CHARLES H. BRADFORD, *Chairman*
JOSEPH S. BARR
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APPENDIX NO 12

REPORT OF THE ADVISORY SUBCOMMITTEE ON MEDICAL EDUCATION

The subcommittee was organized on request of Mr. John J. Desmond, Jr., commissioner of education of Massachusetts, to guide him in licensing trade schools for adjuncts to the medical profession

The Committee met on December 3, 1948, and after careful deliberations, in which the President, President-Elect and Secretary participated as *ex-officio* members, agreed to recommend minimal standards for trade schools in this State. The recommendations were communicated to Mr. Desmond in the following letter

John J. Desmond, Jr., Commissioner of Education
200 Newbury Street
Boston, Massachusetts

Dear Sir

A meeting of the Advisory Subcommittee on Medical Education of the Massachusetts Medical Society was held to discuss the problems as outlined by you in the interview you granted the Chairman. The President, President-Elect and Secretary of the Society were present as *ex-officio* members

The subject of trade schools for training of adjuncts to the medical profession was carefully discussed. It was the consensus of all present that the technical skill required of such adjuncts can be achieved only by proper training and experience acquired in well conducted schools with a proper faculty and supervised work in a hospital. Otherwise, the students cannot become either efficient or reliable and as such may be on the one hand a danger to the public and on the other unable to get and hold positions for which they were trained and spent money and time

The Council on Medical Education of the American Medical Association has established standards for acceptable schools for medical record librarians, for physical-therapy technicians, for medical technologists and for x-ray technicians. Copies of these are included. These standards were unanimously endorsed by this subcommittee as minimal requirements for corresponding schools within this State. It was felt, however, that the admission requirements may be lowered to high school graduates. The importance of a hospital affiliation must be stressed as an absolute necessity

Schools for massage should comply with the requirements for physical therapy technicians

The subcommittee was unanimous in its opinion that no trade schools for electrolysis should be licensed in this State

We refused to take cognizance of the schools for models as not related to medicine

We are deeply appreciative of your earnest efforts to elevate the standards of the schools under your supervision and are anxious to co-operate with you further

Sincerely yours,

I. R. JANKELSON, *Chairman*
Advisory Subcommittee on Medical Education

I. R. JANKELSON, *Chairman*
GEORGE E. GARDNER
RAYMOND H. GOODALE
DONALD A. NICKERSON
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APPENDIX NO 13

REPORT OF THE COMMITTEE ON DIABETES

The special committee on diabetes had two meetings, at which time they made plans for co-operation with the American Diabetes Association's program for diabetes detection and particularly Diabetes Week.

In Massachusetts the Committee distributed to every member of the Society a small four-page bulletin entitled "How to Find and Help the Diabetic Patient in Your Community". In addition, throughout Massachusetts there were a number of radio programs on diabetes detection. Certain of the district societies, at least eight in number, made energetic efforts to carry out testing of urine of many patients in the attempt to discover the untreated diabetic patient, and in addition to obtain the co-operation of the druggists in collecting urine specimens and the co-operation of radio and newspapers in disseminating information. On December 6, 1948, a joint meeting of the Middlesex East, Middlesex South, Norfolk, Norfolk South and Suffolk district societies and the New England Diabetes Association was held in Sanders Theater, Harvard University, Cambridge. The program included eight speakers and was well attended.

A list of the committees appointed in the various districts is appended

The American Diabetes Association's program for Diabetes Week regarded Diabetes Week as merely the initiation of a continuing effort to find the million undiagnosed and untreated diabetic patients in the country and to bring them under the treatment of the medical profession at as early a date as possible. In other areas of the country the steps taken have varied somewhat. In a number of states special committees on diabetes have been appointed by the state societies. In a number of states, district societies have had diabetes committees appointed. However, the main effort was made by local diabetes societies that had been in existence for a few years or were in process of organization, fifty or more in number. Their program varied somewhat, but tended to emphasize special postgraduate training for doctors and education of the lay public by way of radio, newspaper and special meetings, and, finally, diabetes detection through examination of urine or blood of large numbers of patients.

In certain communities highly organized plans are in progress, as in Brookline, Massachusetts, Jacksonville, Florida, and St. Louis, Missouri. Further detection units, in co-operation with the United States Public Health Service, are planned in Wisconsin and West Virginia.

At the time this report is written it is too early to give any quantitative statement about the number of people tested or the amount of publicity given. It may be stated, however, as an incidental fact, that throughout the country 1704 radio stations received a total of 22,000 copies of radio short announcements. Every state and county medical journal received a printed statement, which was sent out through the co-operation of the offices of the American Medical Association.

It is the Committee's opinion that a continued effort should be made to co-operate with national and other state societies to find these diabetic patients and bring them under treatment.

The district societies with committees on diabetes are as follows

Barnstable District

Dr Henry P Hopkins (Chatham), chairman

Essex North District

Dr Robert E. Blais (handling Amesbury and Merrimac)
Dr Lincoln C. Pierce, Newburyport
Dr John J. Hartigan, Greater Lawrence

Hampden District

Dr Eoline C. Dubois (Springfield), chairman
Dr Samuel Fox, Holyoke
Dr Samuel Potsubav, Holyoke
Dr Harold J. Holleran, Westfield

Middlesex North District

Dr Augustine Conroy (Lowell), chairman
Dr George Duvin, Lowell
Dr Joseph Sweeney, Lowell
Dr Leonard Hall, Lowell
Dr Allan L. Schofield, Lowell
Dr Philip G. Berman, Lowell

Middlesex East District

Dr Milton J. Quinn (Winchester), chairman

Norfolk South District

Dr Arthur P. Sullivan, Braintree
Dr Howard S. Reid, Cohasset
Dr John R. Hopkins, Hingham
Dr Frank W. Crawford, Holbrook
Dr Alexander Young, Hull
Dr Robert L. Cook, Quincy
Dr John P. Amerena, Randolph
Dr Arsham Alemlan, East Weymouth

Worcester District

Dr George Ballantyne (Worcester), chairman

Worcester North District

Dr L. B. Thompson, Gardner
Dr Wesley Brown, Petersham
Dr Charles I. Nichols, Baldwinville
Dr M. J. Grossman, Athol
Dr James G. Simmons, Fitchburg
Dr John J. Curley, Leominster
Dr Alton B. Skelton, Winchendon
Dr Clifford Lancey, West Townsend
Dr John W. Mason, Ashburnham
Dr Beatrice Perkins, Westminster

HOWARD F. ROOT, Chairman
FRANK N. ALLAN
GEORGE BALLANTYNE
JOSEPH ROSENTHAL
JAMES L. SNEAD
JAMES H. TOWNSEND
PRISCILLA WHITE

APPENDIX NO 14

SUPPLEMENTARY REPORT OF THE COMMITTEE ON DIABETES

The report printed in the Circular of Advance Information had to be written and submitted to the Secretary within forty-eight hours after the end of Diabetes Week, December 6-12. It was necessarily a preliminary report and suffered from omissions. Since that time, further information has been obtained.

It should first be stated that no quantitative statement can be made about the results of the diabetes-detection drive, in this state or elsewhere, that will be complete because it is undoubtedly true that as a result of the efforts made and the publicity given not only in the medical societies but also by newspaper and by radio, many patients, of whom we have no records, went to doctors' offices for urine tests. Furthermore, many doctors undoubtedly carried out unrecorded tests in their offices. It is also true that in many district societies and towns we do not have a complete statement. Nevertheless, I should like to add to the previous statement the fact that in Bristol South District Dr William Mason headed the committee that divided up their territory, each man having one town. In Fall River just under 600 persons came in for voluntary urine tests. The numbers reported from Worcester, Lawrence and Boston Board of Health, in addition to the extra tests carried out in Brookline, where a long-term detection cam-

paign has been in progress for a year, indicate that fully five or six thousand persons came for urine tests. Probably many of those who had positive urine tests have subsequently been studied by their own family doctors, to whom reports were sent, and blood tests have been done in many cases.

In Brookline the plan set up by the local board of health, with the co-operation of the United States Public Health Service, requires a blood test in every case.

Great credit is due the officers of the New England Diabetes Association, particularly Dr W. R. Ohler and Dr James Townsend, for their efforts to bring about a successful program for the joint meeting of Suffolk, Norfolk, Norfolk South, Middlesex East and Middlesex South in Sanders Theater on December 6. Dr Albert Hornor acted as chairman of the committee appointed by the Boston Health League.

The campaign for diabetes detection in other parts of the United States has made a very auspicious beginning. The important point to remember is that this campaign has been initiated and carried out by doctors. It is not a drive for money. It is purely a public-service effort on the part of doctors, particularly in organized medicine, with the co-operation of public-health agencies, notably the United States Public Health Service, which has received most favorable comment and support of the press, radio and citizens. It is a campaign in preventive medicine initiated by physicians that deserves very energetic prosecution. It should be remembered as brought out on a radio broadcast here in Boston, in which Drs Daniel B. Reardon, John F. Conlin, A. J. A. Campbell and Alfred Frechette took part, that the urine test when it is positive gives a diagnostic clue not only to diabetes but also to a variety of other conditions. It is well-known that glycosuria is often a striking feature of hyperthyroidism. Glycosuria may give the clue to carcinoma, peptic ulcer and coronary-artery disease. Therefore, when this simple laboratory procedure is carried out and the results are given to the family physician and that family physician carries out a complete examination of the patient, discovery of sugar may lead to discovery of other latent conditions and the bringing to that patient of much needed treatment.

It is quite evident that the public-health and the preventive aspects of this diabetes detection drive have been recognized and accepted by newspapers quite generally throughout the country. It is true that in November a printed summary of the diabetes problem was mailed to 5000 editors of the weekly newspapers of the country. Because of their acceptance of the diabetes drive as an effort in preventive medicine by physicians, if doctors through their organized societies will recognize the opportunity presented here for medicine to take the initiative, to obtain the co-operation of public-health agencies and particularly the co-operation of industry and labor, American medicine can perform a genuine service that will win friends and put our public relations on a much better footing.

The Committee on Diabetes of the Massachusetts Medical Society recommends the adoption of the following resolution.

WHEREAS, The surveys conducted in Massachusetts starting with Diabetes Week have confirmed the high incidence of diabetes previously reported, and

WHEREAS, The interest of the public in this phase of preventive medicine was stimulated with noteworthy advantage, and

WHEREAS, The physicians of Massachusetts have shown their willingness to co-operate as individuals and through their district medical societies, and

WHEREAS, The Massachusetts Medical Society has always been noted for its leadership in preventive medicine, therefore be it

RESOLVED, That the president of the Massachusetts Medical Society be requested to appoint a committee on diabetes to follow up the activities undertaken by the Committee on Diabetes Detection, appointed in 1948, and that this committee be authorized to study and develop further activities in co-operation with private and public agencies for the welfare of the diabetic patients in the Commonwealth.

great care. There is no doubt that the work of such a group as this is urgently needed and will be well carried out. The Committee therefore recommends

That the Massachusetts Medical Society support the Bay State Rehabilitation Clinic with a complete endorsement of its program, and offer full co-operation in helping to carry out its important aims

That the first clinic should be inaugurated in Boston, to serve eastern Massachusetts, because of the availability of consultants here and the heavy concentration of industrial groups within commuting distance

That the progress and success of this clinic be used as a guide for opening other clinics in the western part of the Commonwealth as soon as this course should seem practical

That, having discharged its purpose by rendering this report, the present committee be discontinued and replaced by a working committee to be appointed by the President for the purpose of observing the Bay State Rehabilitation Clinic and consulting with its directors and assisting and making recommendations wherever they may prove helpful as new problems are encountered

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APPENDIX NO 12

REPORT OF THE ADVISORY SUBCOMMITTEE ON MEDICAL EDUCATION

The subcommittee was organized on request of Mr. John J. Desmond, Jr., commissioner of education of Massachusetts, to guide him in licensing trade schools for adjuncts to the medical profession

The Committee met on December 3, 1948, and after careful deliberations, in which the President, President-Elect and Secretary participated as *ex-officio* members, agreed to recommend minimal standards for trade schools in this State. The recommendations were communicated to Mr. Desmond in the following letter

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We are deeply appreciative of your earnest efforts to elevate the standards of the schools under your supervision and are anxious to co-operate with you further

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A list of the committees appointed in the various districts is appended

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In certain communities highly organized plans are in progress, as in Brookline, Massachusetts, Jacksonville, Florida, and St. Louis, Missouri. Further detection units, in co-operation with the United States Public Health Service, are planned in Wisconsin and West Virginia

At the time this report is written it is too early to give any quantitative statement about the number of people tested or the amount of publicity given. It may be stated, however, as an incidental fact, that throughout the country 170+ radio stations received a total of 22,000 copies of radio short announcements. Every state and county medical journal received a printed statement, which was sent out through the co-operation of the offices of the American Medical Association

It is the Committee's opinion that a continued effort should be made to co-operate with national and other state societies to find these diabetic patients and bring them under treatment.

tion to Dr James C McCann for his unselfish and tireless efforts in behalf of our interests. In this day and age of momentous threat to our medical independence, we send out a clarion call for 100 per cent enthusiasm and co-operation on the part of the members of the Massachusetts Medical Society in all the problems that affect the Blue Cross-Blue Shield relations with our organization.

CHARLES J E KICKHAM, *Chairman*
JOSEPH C MERRIAM
HARVEY A KELLY
JOHN FALLON
PAUL M BUTTERFIELD

APPENDIX NO 16

REPORT OF THE COMMITTEE ON COUNCIL RULES AND BY-LAWS

To provide a constant authority to which questions of procedure and by-law changes may be referred by the Council for study, this committee offers the following resolution

Resolved, That Chapter IV, Section 3, of the by laws be, and hereby is, amended by the deletion of the "and" (in line 9, page 14) after "Finance" and by the addition under the enumeration of standing committees of the following words, "By-laws and Council Rules"

Resolved, That Chapter VII be augmented by the addition of the following

Section 16 The Committee on By-laws and Council Rules shall consist of five fellows

It shall consider all suggested changes to the rules of the Council and the by-laws of the Society

It shall submit all proposed amendments of the by-laws as provided in Chapter 9 and changes to the Council for action

(Upon the adoption of said resolution all other committees on by-laws and council rules would be replaced)

To provide continuous supervision of the problems of benevolence, the following change in the by-laws is proposed, making the existing group of fellows a standing committee

Resolved, That Chapter IV, Section 3, of the by-laws be, and hereby is, amended by the addition under enumeration of standing committees of the words "and on Benevolence."

Line 9 and line 10, page 14, would then read "Medical Defense, on Society Headquarters, on Finance on Industrial Health, on By-laws and Council Rules, and on Benevolence"

Resolved, That Chapter VII be augmented by the addition of the following

Section 17 The Committee on Benevolence shall consist of five fellows

It shall co-operate with the Massachusetts Medical Benevolent Society in giving aid to fellows of the Society who are incapacitated through no fault of their own, and to their dependents in case of need

It shall operate on an annual budget not to exceed the sum allotted by the Committee on Finance and approved by the Council

It shall remit to the Treasurer all unexpended sums at the end of each year. The Treasurer shall invest such sums in a benevolent fund to be held in reserve for future emergencies

The Committee recommends the creation of a new board to be known as the Advisory Board

This board shall consist of the five most recent past presidents of the Society

To accomplish this, the Committee offers the following resolution

Resolved, That Chapter VIII be, and hereby is, amended by the omission of the words "of trial" from the title

Present section 1 will become section 2, present section 2 will become section 3 a new section 1 will read as follows

The Advisory Board shall consist of the five most recent past presidents of the Society

It shall meet at the request of the President or the Council. The functions of the Board shall be advisory

The Committee recommends that Council Rule 3 be changed to read as follows

These rules may be suspended, changed or discontinued by a vote in the affirmative of two thirds of the councilors present

The Committee recommends that the present Council rules numbered 4, 5, 6, 7 and 8 be changed respectively to 5, 6, 7, 8 and 9, and that a new Council Rule 4 read as follows

It shall be the duty of any committee chairman, submitting a report to the Council, to be present or designate a substitute. The secretary of the Society may be designated unless special background information for informed debate is needed

The Committee recommends the following preamble to Council Rules

Rules and regulations are adopted only to promote orderly and reasonably prompt transaction of business. It is the duty of the presiding officer so to apply them that considered decisions may be reached after free and full debate. They should not be permitted to preclude discussion or subvert action

EDWARD P BAGG, *Chairman*
ELMER S BAGVALL
ALBERT A HONOR
FRANK R OBER

APPENDIX NO 17

REPORT OF THE ADVISORY COMMITTEE TO THE WOMAN'S AUXILIARY

A meeting of the Advisory Committee to the Woman's Auxiliary to the Massachusetts Medical Society was held at 2 00 p m on Friday, October 29, 1948, at 8 Fenway Drs David L Belding, of Norfolk South, Milton J Quinn, of Middlesex East, and John F Conlin, of Suffolk, were present

The Committee in its discussion of a suggested program for consideration by the state auxiliary made a special effort to select fields of activity particularly suited to an organization of physicians' wives interested in promoting the objectives of the Society

Projects were proposed as follows

Organization and extension of district auxiliaries and individual membership

Assistance in supporting and publicizing action of the Society in legislative matters pertaining to medical progress and the public health—as specifically requested. Until state and national legislatures reconvene no specific recommendations can be made. It is anticipated that the Committee on Legislation of the Massachusetts Medical Society may be confronted with consideration of such matters as compulsory national health insurance, antivivisection legislation and a proposal to make animals from public pounds available for medical teaching and research, chiropractic licensing, antivaccination legislation and similar matters. The Legislative Committee of the Auxiliary will be informed of action of the Society's Committee on Legislation

Co-operation with the Massachusetts Health Conference. It is planned to conduct a week-end meeting in February to bring together about 1000 representatives of consumers and suppliers of medical care. This meeting through panels and smaller groups will study numerous phases of health in the Commonwealth and will make recommendations for improvement during the next five years

Health Exhibit in the fall of 1949. This project is designed to bring together visual aids and demonstrations of matters pertaining to health and to circulate the Exhibit through the state's population centers

National Diabetes Week, December 6-12, 1948. Co-operation with the activities of the committee of the Medical Society appointed for this purpose

Affiliation with the Massachusetts Central Health Council. This organization is composed of agencies and various groups working for the advance of the public health. Representation at its meetings would make its clearinghouse facilities on health matters available to the Auxiliary members

Encourage the formation of active local health councils. Increased effort should be made to interest the leaders of community thought and activities in matters affecting medical progress and the health of the community

Health museum. This is a "long range" project. Information will soon be available

Foster increased interest in adult health education

Activities to promote friendly relations with wives of medical students, interns and residents

APPENDIX NO 15

REPORT OF THE SUBCOMMITTEE OF THE EXECUTIVE COMMITTEE ON BLUE CROSS-BLUE SHIELD PROBLEMS

The Committee held a meeting at the Medical Library on Friday, December 10, at 4 00 p m. It has also been represented at the following meetings since the last meeting of the Executive Committee

A meeting of the Blue Shield Central Professional Service Committee at which the past and present organizational relations between Blue Cross and Blue Shield were discussed in considerable detail

A meeting of Blue Shield Fee Committee Chairmen at which the advisability of increasing Blue Shield's schedule of fees, income limitations and subscription rates was discussed

A meeting of New England Blue Cross and Blue Shield Directors (trustees) and administrators, at which Dr Paul Hawley, chief executive officer of Blue Cross and Blue Shield Commissions, explained the proposals to establish a Blue Cross-Blue Shield Association and Health Service, Inc., for the purpose of facilitating the enrollment of national accounts

A meeting of Massachusetts delegates to the American Medical Association and representatives of Blue Shield prior to the St. Louis meeting of the House of Delegates at which the proposals to establish a Blue Cross-Blue Shield Association and Health Service, Inc., were discussed in detail. In addition the Committee has attempted to be familiar with all related aspects of the subject and to keep the voting membership of the Blue Shield, Executive Committee of the Council and the members of the Society informed about Blue Cross and Blue Shield problems

The Committee has been advised unofficially that the following action affecting Blue Cross and Blue Shield was taken at the American Medical Association Interim Session at St. Louis (November 30 to December 3, 1948). The House of Delegates approved the entire report of the Reference Committee on Medical Service and Pre-payment Insurance Plans on Wednesday, December 1, 1948. Dr L S McKittrick, of Massachusetts, was a member of this Reference Committee. An abbreviated report follows resolutions introduced by the Michigan State Medical Society and the Ohio State Medical Association approving the proposals for the establishment of a Blue Cross-Blue Shield Association and a Blue Cross-Blue Shield Health Service, Inc., were discussed for three hours on the morning of December 1. The Reference Committee report follows: "The Committee is in entire accord with the necessity and advisability of extending medical care and coverage of all classes of our population. Your Committee does not believe that sufficient factual data has been supplied to enable it to make an intelligent decision on this most important subject. Therefore, these resolutions are not approved."

A resolution introduced by Oregon called upon the American Medical Association to sever its relations with Associated Medical Care Plans and dissolve itself from any further responsibility for Associated Medical Care Plans' activities. The Reference Committee report was "Disapproved."

The Council on Medical Service introduced a supplemental report on the Associated Medical Care Plans' proposal to form a national insurance company, which contained the following recommendations to the House of Delegates: approve the formation of a national enrollment agency and disapprove the proposal for the formation of a national insurance company, approve the statement delineating the field of operation of the council and A M C P, which was presented to the Board of Trustees in December, 1946, and approved by the Board, but not approved by the A M C P Commission, recommend that A M C P make necessary changes in its Constitution and by-laws that would take A M C P out of the policy-making field and reaffirm the Council's authority to promote the voluntary prepayment plan program in America

The Reference Committee report was "Supplemental Report of the Council on Medical Service relative to the Supplemental Report on A M C P. Proposal to form a national insurance company was carefully reviewed. Your Reference Committee recommends the adoption of the Supplemental Report with the following addition to paragraph

1 of the recommendations (Page 4) 'further development of co-ordination of and reciprocity among local plans'."

A resolution on policy reaffirming the A M A's belief in the application of the principle of medical care insurance on a voluntary basis was introduced by California. The Reference Committee made a few changes in wording, and then recommended adoption

This subcommittee is of the opinion that rejection of the proposed Blue Cross-Blue Shield Association and Health Service, Inc., by the House of Delegates still leaves the door open to voluntary co-operation by the Blue Shield plans with a health service, incorporated, which will probably be established by Blue Cross alone. As a matter of good business it seems that such co-operation would be desirable

The Committee is of the opinion that approval by the House of Delegates of the statement delineating the fields of operation of the Council and A M C P that was presented to the Board of Trustees in December, 1946, and approved by the Board, but not approved by the A M C P Commission, may result in disintegration of A M C P inasmuch as the primary concern of this organization is to be physical setup of plan offices and service equipment, personnel setup of plans, standardization of methods or systems of keeping actuarial data on plan experience, standardization of forms used by plans, uniformity of contracts and provisions for reciprocity among plans, and methods and mediums to be employed in selling and so forth

There is no question that A M C P in the three years since its founding has done an outstanding job of promoting and extending the voluntary prepayment principle throughout the United States. If this organization is to be reduced to an informational bureau it is not unlikely that the initiative of its members, who, after all, know more about prepayment than any other group in organized medicine, will be seriously damaged

A controversial aspect of the Blue Shield relation with the medical profession is the problem of fees for service. Obviously, there is bound to be some difference of opinion and at times dissatisfaction in this regard, on the part of both the Blue Shield's officials and the participating physicians. It is the opinion of the Committee that a mechanism should be established that would tie the fee committee closer to the Society. As a result of discussions with Blue Shield officials, the Committee recommends that a general chairman of Blue Shield's Committee of Fee Committee Chairmen be appointed annually by the president of the Massachusetts Medical Society, that the executive director of Blue Shield annually request the specialty sections within the Society and the specialty sections without the Society to review the composition of their respective Blue Shield fee committees, and that the executive director of Blue Shield suggest to the specialty sections a uniform method of rotating membership on Blue Shield committees

The antitrust suits now pending in Oregon and San Diego, California, interest the Committee. It has come to our attention, however, that the Blue Shield is reviewing its policies particularly in regard to payment of nonparticipating physicians, retention of subscribers who leave the Commonwealth and sales policy toward Blue Cross

It seems that the actions pending in Oregon and California are directed at medical-society policies rather than at medical care plan operations. Therefore the Subcommittee recommends that the Massachusetts Medical Society, through its appropriate committees, review its policies in the light of the antitrust proceedings against the Oregon State Medical Society and the San Diego County Medical Society

The Committee wishes to advise that the Blue Shield Board of Directors has appointed Dr Charles G Hayden to the position of executive director, thus crystallizing an administrative relation that has existed for the past three years. The Committee heartily approves this strengthening of administrative responsibility

We have been informed that Blue Shield has received many requests from participating physicians for membership in its Services. In view of the present policy of the Society such membership has not been accepted. The Committee plans to investigate this subject further and will report at a later date concerning its deliberations

In conclusion, the Committee cannot possibly allow this occasion to pass without an expression of heartfelt apprecia-

rant No masses or organs were palpable No dorsalis pedis or posterior tibial pulsations were felt Both feet were cold The calves were not tender

The temperature was 97°F, the pulse 70, and the respirations 20 The blood pressure was 80 systolic, 60 diastolic

Examination of the blood showed a hemoglobin of 13.2 gm and a white-cell count of 10,500, with 62 per cent neutrophils, 32 per cent lymphocytes and 4 per cent monocytes Platelets were normal The urine was normal The sedimentation rate was 105 mm per minute, corrected to 0.81 mm per minute The hematocrit was 41 per cent The prothrombin time was 15 seconds (control, 15 seconds) The nonprotein nitrogen was 19 mg and the serum protein 4.63 gm per 100 cc, with an albumin-globulin ratio of 1.85 The cephalin flocculation and serum amylase were well within normal limits In the plain film of the abdomen a rather diffuse haziness suggested the presence of fluid Several slightly dilated loops of small intestine were seen in the upper abdomen No intra-abdominal calcification was visible

In the hospital there were several attacks of gaseous distention and epigastric pain They usually responded to codeine and chloral hydrate On the fourth hospital day there was a new area of hemorrhage in the skin of the neck following slight trauma, otherwise his condition remained unchanged Further laboratory examinations made in an effort to discover the cause of bleeding were not very helpful The bleeding time was four minutes, the clotting times in the first to fifth tubes were 8, 9, 10, 10 and 10 minutes, respectively A tourniquet test was negative The blood vitamin C level was 1.6 mg per 100 cc No evidence of serum at the end of forty-five minutes of liver failure could be obtained, and only 4 per cent bromsulfalein remained in the serum at the end of forty-five minutes The stools contained no blood and no undigested muscle The neutral fat was normal Soaps and other fat combinations were +++ On x-ray examination both pleural cavities contained free fluid No intrinsic lesion of the upper gastrointestinal tract could be made out by x-ray study, but there was thought to be evidence of a lobulated pressure defect against the second and third portions of the duodenal loop without definite involvement of the mucosa The diffuse ground-glass density of the abdomen remained

On the twenty-fourth hospital day edema developed in the scrotum and penis On the same day an exploratory laparotomy showed about a pint of clear straw-colored fluid The most striking finding was the ease with which all the tissues bled when handled This was especially true when the small bowel was handled There were no adhesions The pancreas was not seen but felt perfectly normal The liver and spleen also looked normal Toward the end of the operation the pa-

tient developed marked edema of the larynx, which was probably due to the trauma of the intratracheal tube, and this necessitated a tracheotomy

The immediate postoperative condition was good Several transfusions had been given during the procedure On the following day the patient suffered marked respiratory difficulty Rutin was started in an attempt to reduce capillary bleeding On the second postoperative day he was pale and breathing with difficulty He gradually became weaker The blood pressure fell to 60, and the pulse rose He died on the same day

DIFFERENTIAL DIAGNOSIS

DR WALTER BAUER I have bet ten to one that the pathologist cannot make a positive diagnosis in this case We shall see if he can

The skin lesions were never raised?

DR CHESTER M JONES That is right

DR BAUER The hemorrhagic discoloration was only in the region of the molars Is that right?

DR DANIEL S ELLIS He had some on the buccal surfaces, and also one on the tongue

DR BAUER I think it is very important to have a good description of the gums in this case, because one might want to entertain the diagnosis of monocytic leukemia However, I do not think this is the diagnosis

Nothing is said about reflexes or the neurologic findings

DR JONES They were normal

DR BAUER Can we accept the statement that this forty-nine-year-old man had no pulsations in his feet? Is this correct?

DR JONES We could not find them

DR BAUER Did the monocytes ever go any higher than 4 per cent?

DR JONES No

DR BAUER Did he exhibit an eosinophilia?

DR JONES He never had an eosinophilia

DR BAUER The smear remained essentially the same throughout the illness?

DR JONES There were no subsequent smears done

DR BAUER I assume that a bone-marrow biopsy was not done Is this correct?

DR JONES There was no biopsy of the bone marrow

DR BAUER I take it that the pleural spaces were never aspirated

DR JONES No

DR BAUER I wonder if I might ask why the surgeon kept a drainage tube in the gall bladder Did he drain it because of the alterations noted in the second and third portions of the duodenum? Was the gall bladder drained because of an acute pancreatitis? Was he treating an acute cholecystitis or trying to prevent it and thereby prevent another attack of pancreatitis? I presume that the surgeon thought the patient had pancreatitis but was unable

Assist in making the facilities of the Boston Medical Library and other deposits of medical literature more widely available to the medical profession

Study problems concerning the shortage of nurses and other matters pertaining to the nursing profession

Study conditions pertaining to the care of the aged and the chronically ill

Obtain familiarity with such problems relating to health in the community as housing, food and restaurant sanitation, industrial hygiene and school health

Study such problems relating to medical practice as the physician's hours of work, hospital staff appointments, night calls, days off, medical meetings, vocations and other matters that have an influence on the physician's family life

An interesting study might concern itself with statistical data on the budgeting of the physician's time. How much time is spent in attending patients without charge in office, clinic or hospital? How much time is spent in medical reading, giving and attending lectures, attending medical meetings and so forth?

Study of the basic economic factors affecting costs of medical care and such related problems as the differentiation between the cost of medical care rendered in the hospital and in the physician's private practice

JOHN F. COLLIN, *Chairman*
DAVID L. BELDING
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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 35141

PRESENTATION OF CASE*

A forty-nine-year-old tanning-factory superintendent was admitted to the hospital because of abdominal pain.

Seven months before admission, having been previously well, the patient began to have attacks of abdominal pain. The pain, which was always located in the epigastrium just above the umbilicus, was severe, knifelike in character rather than colicky, and did not radiate. It began after breakfast and usually continued for two or three days, it was not affected by lunch or supper. There were periods of four or five days when the pain was absent. The pain was not affected by position, did not prevent sleep and kept him from work about two days of each week. X-ray films were said to show an ulcer at the duodenum, but an ulcer diet failed to improve the symptoms. Subsequently, x-ray films demonstrated the ulcer once but failed to show it another time. There was no nausea or vomiting. The bowels, previously regular, became constipated. There were no foul or foamy movements and no black or tarry stools. His weight fell from 185 to 150 pounds. He also noticed an increased tendency to easy bruising, which he had previously had. Mere rubbing of his eyelids produced a red color, which took about three days to be absorbed. Red spots also appeared on the face and neck. These were

never painful, and there was no swelling. Four months before admission he had a particularly severe attack, and an exploratory laparotomy at a community hospital revealed a considerable quantity of bloody fluid. No ulcer was seen. A drain was inserted in the gall bladder. This drained black and later green fluid and finally dried up three months later. The gall bladder was said to have been perfectly normal. The patient required one transfusion.

Following operation he continued to have attacks of abdominal pain as before. He was home for six weeks but returned to the hospital because of pain in the drainage wound. He remained in the hospital about three weeks and was discharged, two weeks before entering the Massachusetts General Hospital. During these two weeks the former pains subsided, but gas pains became more severe and constituted the chief complaint on admission. A diet eliminating fats made no difference in the pain. There was no jaundice, light stools, dark urine or chills or fever. Itching of the skin was noticed in the three months before admission.

The patient had been gassed and temporarily blinded in World War I. There were no sequelae except a chronic productive cough. He suffered some shortness of breath in recent years. Two years before admission, after an episode of sudden weakness and dizziness, he was found to have a low blood pressure and anemia. With iron and liver therapy his blood improved. After this he always noted some red spots, especially on the eyelids and other parts of the face. These were brought on by slight trauma and lasted about three days. There were no other evidences of easy bleeding.

Physical examination showed the patient to be alert and in no great discomfort. There were many excoriations over the arms, neck and upper back. There were also many 3-mm to 4-mm red blotches over the neck and face. These had an irregular outline, and were nontender and not raised. Areas of hemorrhage discolored the buccal mucosa and formed bluish, spongy swelling around the bases of the molars. Small, nontender lymph nodes were palpable in the left axilla and the groins. The heart and lungs were normal. On the abdomen there was a 12-cm scar to the left of the midline in the upper quadrant and a 6-cm scar in the right upper quad-

*Discussed May 1, 1947

ings The disease may occur at any age and in both sexes but is usually a disease of young people

I know of no other disease that would give this clinical picture Though I say I would like to make a diagnosis of periarteritis nodosa, there is not sufficient evidence in the way of clinical findings to substantiate this diagnosis The patient never had hypertension, abnormal urinary findings, neurologic abnormalities or evidence of serous-membrane involvement I well appreciate that some cases of periarteritis nodosa can affect only one organ We have seen patients who had arterial lesions, confined primarily to the pancreas, with minimal or few lesions elsewhere The initial attack of pain might be interpreted as due to periarteritis nodosa, with a saccular aneurysm in the pancreas that ruptured This would explain the free fluid in the abdominal cavity Yet he did not have pancreatitis I shall say that this man did not have periarteritis nodosa Furthermore, I do not believe that the pathologist can make a diagnosis and prove it beyond a point of doubt I think this patient had one of the diseases that Osler included in the erythema group I should be glad to answer questions and be more than happy to receive helpful suggestions

DR CASTLEMAN Were any autopsies performed in the cases that Osler described?

DR BAUER I am sorry to say that I waited until last night to read the case history, and I found my library inadequate on this point

DR JONES It was curious that one could palpate the neck and cause a hematoma, and yet a tourniquet on an arm did not produce bleeding

DR BAUER Some doctors feel very hard

DR JONES We were advised not to, so we did not

DR WYMAN RICHARDSON How about the low serum proteins?

DR BAUER I cannot explain this finding

DR JONES We had him on an adequate diet

DR BAUER He had bled from time to time and may not have been in good enough condition to regenerate proteins

DR RICHARDSON I think he may well have had something wrong with the liver

DR BAUER I agree — as part of a generalized capillary disease

A PHYSICIAN Can the abdominal pain be explained by infiltration of blood where it came in contact with the peritoneum — would that not give periodic attacks?

DR JONES The pain was very intense

DR BAUER Dr Short, you are the person who called this group of diseases to our attention What about it? Does it belong in Osler's group or not?

DR CHARLES L. SHORT I do not know

DR BAUER I think it is unfortunate that we use such ill defined terminology It is a reflection on us as much as on the pathologist

DR CASTLEMAN I have not spoken yet

DR BAUER I think you are going to talk about this group of diseases and that we will not agree on terminology

DR SHORT Is it Henoch's disease?

DR BAUER It is one of the diseases Osler included in the erythema group Whether it is Henoch's purpura or not, I do not know One can only say that the capillaries were abnormal It has been called by all sorts of names, and no one of them tells us anything about the mechanism or the etiology

DR ELLIS Do you think he had disseminated lupus erythematosus?

DR BAUER No, I do not

DR JONES His physician made a pertinent remark He wanted to know why we did not find albumin They found it when the patient was in the other hospital and at home on several urinary examinations I think he did show a + or ++ test on occasion, but the rest of the time the urine was normal

DR BAUER I shall re-emphasize one point — the description of the skin lesions and the recurrence of abdominal pain is classic for this disease, it fits it to a "T" as far as I am concerned

CLINICAL DIAGNOSIS

Acute disseminated lupus erythematosus

DR BAUER'S DIAGNOSIS

Osler's disease—"Erythema group of skin diseases with visceral manifestations"

ANATOMICAL DIAGNOSES

Primary systemic amyloidosis, involving myocardium, cardiac valves, lungs, spleen, lymph nodes and blood vessels

Purpuric hemorrhages of skin, intestines and peritoneum, severe

Cardiac hypertrophy and dilatation

Renal infarcts, recent, left

PATHOLOGICAL DISCUSSION

DR CASTLEMAN Our findings on examination of the abdominal cavity were almost the same as those at exploration There were subserosal hemorrhages in the wall of the small bowel, as well as submucosal hemorrhages throughout the entire gastrointestinal tract The spleen and liver looked perfectly normal, as did the pancreas The kidneys were perfectly normal in size and appearance except for a few, small, recent infarcts in the left kidney The heart was enlarged, weighing 450 gm, and on the valves were small white spots, which seem like artifacts on this photograph of the aortic valve (Fig 1)

to establish the diagnosis at the time of the exploration. Is this correct?

DR JONES Yes

DR BAUER I do not believe that he had pancreatitis, but I may be wrong

May we see the films? They describe a diffuse ground-glass appearance, which is evidently due to fluid

DR TOUFIC KALIL This shows the ground-glass appearance and the separation of the loops of small bowel consistent with fluid. There is fluid in both pleural spaces going into the fissures

DR BAUER This patient never had pleurisy?

DR JONES No

DR BAUER And no pericardial friction rub?

DR JONES No

DR KALIL This is the gastrointestinal series. There is a pressure defect on a loop of the duodenum. The nodularity described is present here in the second and third portions

DR BAUER How would you interpret the distortion?

DR KALIL It is perhaps due to increase in size of the pancreas. The mucosa of the duodenal loop is all right

DR BAUER That neither helps me nor disturbs me. The pancreatic enzymes were normal

The abdominal fluid and the edema of the scrotum and penis can be explained on the basis of the hypoproteinemia. I wonder why he was explored. Was it because of an attack of pain or other change in clinical course, or is it unfair to ask?

DR JONES No. He continued to have attacks of pain, without elevation of temperature, pulse or respirations. The pain was severe and required opiates. There was no rigidity or tenderness at the time of the attack of pain. The pain was always in the same place—in the midepigastrium and went through to the back

DR BAUER Is it known whether he had fever or leukocytosis in the first hospital?

DR JONES My impression is that he had no fever

DR BAUER The other interesting finding at operation was the ease with which the tissues bled when handled. Was there hemorrhage in the serosa, or was bleeding observed in all tissues of the abdomen?

DR JONES There were several serosal hemorrhages when the abdomen was opened and not due to handling

DR BAUER Did they appear also on handling?

DR BENJAMIN CASTLEMAN Dr Richard H. Sweet said that when he elevated a loop of small bowel there was diffuse oozing over the surface of the small bowel

DR BAUER That is the whole small bowel?

DR CASTLEMAN In spots, oozing here and there

DR BAUER I shall take that for what it is worth. The first thing I wondered about as I read the history was whether or not there was any likelihood of benzol poisoning since he had worked in a tannery and may have been exposed to benzol. However, we do not know the kind of tannery or whether benzol was used. Because of his occupation this diagnosis should be considered, however, as one reviews the history one sees little reason for entertaining this possibility

We are dealing with a man forty-nine years of age, who exhibited three findings we must account for. The fourth, the absence of pulsations in the feet, may not have been related to the primary disease. I wish the pulsations had been felt because the other findings—recurrent purpura lasting only a few days and attacks of abdominal pain—are consistent with a diagnosis of purpura. The abdominal pain lasted only a few days at any one time. The abdomen was opened and contained free bloody fluid. When confronted with a patient with symptoms suggesting diffuse vascular disease, in this case the capillaries, we entertain the diagnosis of periarteritis nodosa. However, there is very little to substantiate this diagnosis. He never had fever or a leukocytosis. In fact, there was very little to suggest the presence of periarteritis nodosa except recurrent attacks of abdominal pain. He did have free bleeding in the abdominal cavity on one occasion, and one might say it was due to rupture of a saccular aneurysm of the type seen in people with periarteritis nodosa. At the second operation it was observed that all tissues bled very easily when handled. This finding is not easily explained on the basis of periarteritis nodosa or on the basis of related or so-called "group disease." I hate to talk about "group disease" because the term can be used as a catch-all. We do not know too much about the pathogenesis of "group disease" (rheumatoid arthritis, rheumatic fever, disseminated lupus, dermatomyositis, periarteritis nodosa and scleroderma). I think this man had the disease described by Osler, Henoch and Schönlein. He falls in the group that Osler^{1,2} spoke of as the erythema group. Erythema multiforme exudativum and Henoch's purpura are included in this group, but, as Osler said, the clinical manifestations of patients included in the erythema group vary greatly, particularly the cutaneous lesions. This term, however, is merely a blanket term and can cover a multitude of sins. These people give a history not unlike that of this patient and may have arterial symptoms in addition. They are very apt to have bleeding into the gastrointestinal tract and may give a history of repeated bloody stools. This patient evidently never had the latter, however, I do not believe that the absence of this finding should disturb us, nor should the absence of arterial find-

stains. The note is made in a number of articles that the iodine stain is negative and that the Congo red is positive. That was true here. The involvement of the endocardium has been described a number of times and was very characteristic in this case.^{3,4} I believe this is the first case in which we have seen amyloid involvement of the cardiac valves.

DR BAUER: I should still like to take exception. As yet we cannot say that amyloid disease is a complication of rheumatoid arthritis. It may be due to the same mechanism responsible for rheumatoid arthritis.

I do not think that you have necessarily proved that we are dealing with primary amyloidosis in

DR CASTLEMAN: Yes. As yet we have not found a better answer. I suppose the cases that Osler described were not associated with amyloid.

DR BAUER: I wish we knew the autopsy findings in such cases. It may be that people with primary

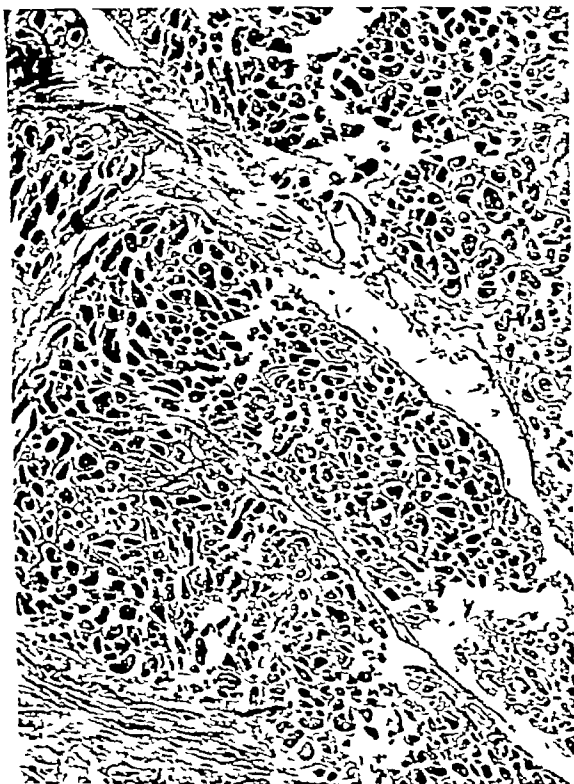


FIGURE 3 Amyloidosis of the Myocardium

this case, although there is an increasing amount of evidence that patients with diffuse vascular disease are prone to have amyloid disease.

DR CASTLEMAN: It may be true that amyloid associated with rheumatoid arthritis is all primary, but its distribution is similar to the secondary type. Certainly, the particular anatomic findings in this case are what have been seen in a large number of cases.

DR BAUER: In what has been called primary amyloid disease?



FIGURE 4 Photomicrograph of the Intestine Showing Amyloidosis of the Walls of the Submucosal Blood Vessels Surrounded by Hemorrhage

amyloidosis initially have primary vascular disease. However, this is a guess. We ought to look up the literature and see if autopsy of long-observed cases of so-called Osler's disease showed primary amyloidosis.

DR CASTLEMAN: But until we find out what the primary disease is we have to place this case in the so-called primary atypical amyloidosis group.

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This is a slide of the mitral valve (Fig 2), and it shows exactly the same granules, some extending up on to the auricular wall where there were a few, small, submucosal hemorrhages and going down along the chordae tendineae, which were not, however, thickened or involved with an old process. Similar granules were found on the other valves. When we first looked at these on gross examination we thought they were similar to those seen in lupus erythematosus. The granules, however, were not

infection, rheumatoid arthritis and a few other conditions. In this type the amyloid infiltration affects almost always the liver, spleen and kidneys. Then there is the so-called primary systemic amyloid disease in which no definite primary disease can be observed anatomically. In this type the amyloid infiltration very rarely affects the liver, spleen and kidney but may affect the heart and lungs primarily, often with diffuse involvement of the vessels throughout the body. That was true in this case. The most marked involvement was in the heart and in the lungs and in the vessels throughout the body. There was a little infiltration of the spleen, which has been reported in so-called primary systemic amyloidosis. It was present, as one can see, throughout the submucosa of the intestine, and these patients very often have hemorrhages. In



FIGURE 1 Aortic Cusps, Showing Amyloid Deposits

so large as those seen in Libman-Sachs endocarditis and were more numerous.

This is a microscopical slide of one of these valves showing the amorphous, very pale-pink appearance. A Congo-red stain of the valve demonstrates that all the material on the cusps is amyloid. The endothelium itself is perfectly normal. It is interesting that amyloid stains of the liver and kidney were negative. Here is a section of lung showing amyloid infiltration of the walls of the small vessels. It is interesting that the usual iodine stain for amyloid was negative, but the Congo-red stain was positive. The heart muscle was extensively involved with amyloid (Fig 3). The cause of the hemorrhages is well seen in the section of the small intestine (Fig 4). Here is the normal mucosa, here is a submucosal hemorrhage and in it are all these small arteries extensively infiltrated with amyloid. There is diffuse amyloidosis of the arteries throughout. This case, therefore, is characteristic of the so-called primary systemic amyloidosis, not the secondary type.

DR. BAUER: How can you prove that it was primary amyloidosis and not due to another disease?

DR. CASTLEMAN: There are two main types of amyloid disease. One that we all know about is the secondary type of amyloidosis due to chronic



FIGURE 2 Mitral Valve, Showing Amyloid Deposits Extending over the Endocardium and Chordae Tendineae

the cases of primary systemic amyloid disease described in the literature, about 40 per cent are prone to bruise easily, probably owing to the fact that the amyloid infiltration of the vessels makes the vessels more vulnerable to trauma.³ I think one can argue the point and say that this is not a primary disease but is secondary to a disease that we cannot recognize anatomically. The amyloid distribution, however, is quite different from the so-called secondary amyloid disease. Another thing that is common in the primary form is that this type of amyloid does not always take up the usual amyloid

150 mg, total protein 7.11 gm, albumin 5.06 gm and globulin 2.05 gm per 100 cc. The patient grew progressively weaker despite frequent transfusions and intravenous fluids. He vomited at any attempt to eat and, although perfectly oriented, was drowsy much of the time. Hematuria and pyuria persisted. On the thirty-eighth hospital day the nonprotein nitrogen was 101 mg per 100 cc. Two days later he took a marked turn for the worse, with bleeding at all orifices. On the following day he died.

DIFFERENTIAL DIAGNOSIS

DR WALTER BAUER: If this man had difficulty keeping his food down for one year the weight loss could be accounted for on the basis of an inadequate caloric intake.

One would also like to know whether the gastrointestinal symptoms twenty-five years previously and those experienced during the four weeks prior to entry were causally related.

I assume that the diastolic murmur heard along the left border of the sternum was transmitted from the aortic area, although it is of interest that the examiner described both a blowing diastolic murmur and a Grade I whine.

I assume that the specific gravity of 1.015 is the highest recorded.

DR TRACY B. MALLORY: One specific gravity was 1.022, and the others ranged from 1.010 to 1.015. Someone put down a question mark against the 1.022 figure, however.

DR BAUER: I shall assume that the specific gravity of 1.015 represented the ability of the kidneys to concentrate.

Was there any increase in cells in the spinal fluid? Was the spinal-fluid protein increased?

DR MALLORY: The protein is recorded as 38 mg per 100 cc by the electrophoretic method and 42 by the old method.

DR BAUER: There was no mention of cells?

DR MALLORY: Yes, I see a note saying that there were 3 cells per cubic millimeter.

DR BAUER: Are there any x-ray films of the knee?

DR STANLEY M. WYMAN: No. The chest films show an apparently normal upper lung. The heart shadow is increased in transverse diameter, with prominence of the apical portion, probably representing an enlarged left ventricle. The aorta is prominent in the ascending portion and shows a suggestion of bulging but no calcification in this portion of the aorta or elsewhere in its thoracic course.

DR BAUER: Would you care to say anything further about the aortitis?

DR WYMAN: It certainly is suggestive of aortitis. Examination of the stomach shows a crater on the lesser curvature at the angle. An additional finding not noted in the original record is a deformed duodenal cap, which although present, is not well

demonstrated in this film. There is a suggestion of a filling defect in the prepyloric region, which is better seen at the examination done seventeen days later.

DR BAUER: A prepyloric crater as well as one on the lesser curvature?

DR WYMAN: It is suggestive.

DR BAUER: Nothing is said about that in the abstract.

DR WYMAN: No. These spot films show the decrease in size of the crater on the lesser curvature. The next two films selected from the pyelogram examination are not satisfactory for fine detail, but they show excretion of dye in fairly good concentration without gross distortion or dilatation.

DR BAUER: Would you say that the patient excreted the normal amount of dye?

DR WYMAN: I think he did well for a man of seventy-five.

DR BAUER: With a specific gravity of 1.015?

DR WYMAN: Very well indeed.

The film of the skull shows no demonstrable bone disease. These films of the long bones, the lower legs and forearms reveal no definite bone destruction. The joint spaces, the wrists and the ankles appear essentially normal.

DR BAUER: The question is, How many diagnoses should one make? Can all the findings be explained on the basis of one disease? I do not believe so. I think there can be no doubt that this man had multiple myeloma. The evidence for that is clear-cut and certainly adequate. It is reported that the electrophoretic studies failed to reveal Bence-Jones protein in the serum. This, however, has been true of other cases of multiple myeloma. Likewise, a hyperproteinemia and a hyperglobulinemia are not always present.* I think that this man probably had a complication seen in multiple myeloma—namely, amyloidosis. There are, of course, three kinds of amyloidosis: primary amyloidosis, amyloidosis associated with multiple myeloma and secondary amyloidosis. Visceral involvement is much less frequent in the first two, and the staining reactions for amyloid are variable and atypical. It is also of interest that in most cases of primary amyloidosis in which the total serum proteins have been determined they have been found to be essentially normal.* In amyloidosis associated with multiple myeloma Bence-Jones proteinuria is present in only about half the cases. To establish the exact incidence of primary amyloidosis one must suspect and if possible rule out myeloma in all cases of amyloidosis in which no obvious cause is found.

This man had a positive blood Hinton test, spinal-fluid abnormalities, enlargement of the left ventricle, evidence of aortic-valve incompetence and enlargement of the ascending portion of the aorta. Therefore, I would like to make the additional

*Done by the Howe technic.

CASE 35142

PRESENTATION OF CASE

A seventy-five-year-old Portuguese laborer was admitted to the hospital because of epigastric pain, anorexia and loss of weight.

The patient had quit work one year before entry because of weakness, but stated that he had been well up until about two months before admission. His weight had fallen from 154 to 127 pounds. At the same time he had painful, swollen knees, but this complaint had disappeared. Three or four weeks before admission he began to experience intermittent, nonradiating, "burning" pain in the middle and left epigastrium, which occurred half an hour to one hour after meals. The pain was very sharp for ten or fifteen minutes and then wore off. Occasionally, the pain reappeared between meals. Milk and food seemed to relieve it for a while, as did belching. Sometimes he vomited a small amount with relief. There were no changes in bowel habit, and he did not notice the color of the stool. There was no hemoptysis. There was no jaundice, distention, dysphagia or prominent genitourinary symptoms. There had been recent mild ankle edema. A physician had given him pills and a white liquid for the pain, but these gave no relief. Diet during the present illness had consisted of tea, toast, soups and juices.

About twenty-five years before entry he had suffered episodes of epigastric pain which he could not clearly describe. He continued to work, and eventually these wore off without medication. Several years later he underwent an appendectomy. He denied the symptoms or treatment for syphilis or gonorrhea.

Physical examination revealed a pleasant, elderly man, showing signs of weight loss. There was no jaundice. There was a cataract in the left eye. There were a few, shotty, firm lymph nodes in the axillas, especially on the right. There were prominent inguinal chains bilaterally. The lungs were clear. The heart was boot-shaped, with the point of maximal impulse at about the midclavicular line. There were occasional premature beats, and the aortic second sound was greater than the pulmonary. There was a Grade I, blowing diastolic murmur loudest in the aortic area, a Grade I whine in diastole along the upper left sternal border, and a Grade II systolic murmur heard loudest at the apex but also heard in the axilla and at the base. The abdomen was flat, with normal peristalsis. There was an appendectomy scar in the right lower quadrant. There were no palpable masses or tenderness. The liver edge was palpated one fingerbreadth below the right costal margin on inspiration and was prominent across the epigastrium. There was a + ankle edema.

The temperature was 99°F, the pulse 96, and the respirations 18. The blood pressure was 146 systolic, 70 diastolic.

The urine had a specific gravity of 1.015 and gave a +++ test for albumin, and the sediment contained a few white cells and a rare hyaline cast. Examination of the blood disclosed a red-cell count of 2,570,000, with a hemoglobin of 7.5 gm, and a white-cell count of 17,000, with 27 per cent neutrophils, 67 per cent large lymphocytes and 4 per cent monocytes. Anisocytosis and hypochromia were noted. The stools gave a ++ guaiac reaction. The blood Hinton test was positive. The serum protein was 6.20 gm per 100 cc, with an albumin of 3.86 and a globulin of 2.34 gm (albumin-globulin ratio of 1.7). The nonprotein nitrogen was 27 mg, phosphorus 3.7 mg, and alkaline phosphatase 3.5 units per 100 cc. The prothrombin time was 24 seconds (normal, 16 seconds), the cephalin flocculation test was negative in twenty-four and forty-eight hours. A gastric aspiration showed free hydrochloric acid.

The patient's condition remained essentially unchanged. A gastrointestinal series revealed a grossly benign ulcer crater, 1.5 cm in diameter, approximately 1 cm beyond the lesser curvature of the stomach. A roentgenogram of the chest showed a heart enlarged in the region of the left ventricle. The aorta was somewhat widened, particularly in the ascending portion. On the fourth hospital day urine gave a ++++ test for albumin, and the sediment contained many red cells, with an occasional white cell and hyaline cast. A blood smear showed 8 per cent plasma cells, and a subsequent sternal-bone-marrow aspiration disclosed a marked diminution of myelopoiesis and erythropoiesis. About 80 per cent of the cells were mature plasma cells, with a few blast forms and binucleated plasma cells. Bence-Jones protein was found to be abundant in the urine. Roentgenograms of the skull, forearms, wrists and hands showed no evidence of bony disease. On intravenous pyelogram the kidneys excreted the dye promptly and outlined nondilated calyces, pelvis and ureters. A serum protein electrophoretic separation produced a normal pattern, indicating the absence of Bence-Jones protein in the serum. The spinal-fluid goldsol curve was 000034+211. A urine culture showed colon bacilli and a few nonhemolytic streptococci. On the eleventh hospital day the patient stated that he no longer had epigastric pain but that he did feel weak "all over." Five days later the white-cell count was 47,800, with 22 per cent neutrophils, 44 per cent large lymphocytes and 34 per cent small plasma cells. On the nineteenth hospital day a gastrointestinal series showed that the gastric ulcer had decreased considerably in size. The stools became black and gave a ++++ guaiac reaction. The blood calcium was 10.6 mg, phosphorus 9.2 mg, phosphatase 3 units, nonprotein nitrogen

150 mg, total protein 7.11 gm, albumin 5.06 gm and globulin 2.05 gm per 100 cc. The patient grew progressively weaker despite frequent transfusions and intravenous fluids. He vomited at any attempt to eat and, although perfectly oriented, was drowsy much of the time. Hematuria and pyuria persisted. On the thirty-eighth hospital day the nonprotein nitrogen was 101 mg per 100 cc. Two days later he took a marked turn for the worse, with bleeding at all orifices. On the following day he died.

DIFFERENTIAL DIAGNOSIS

DR WALTER BAUER: If this man had difficulty keeping his food down for one year the weight loss could be accounted for on the basis of an inadequate caloric intake.

One would also like to know whether the gastrointestinal symptoms twenty-five years previously and those experienced during the four weeks prior to entry were causally related.

I assume that the diastolic murmur heard along the left border of the sternum was transmitted from the aortic area, although it is of interest that the examiner described both a blowing diastolic murmur and a Grade I whine.

I assume that the specific gravity of 1.015 is the highest recorded.

DR TRACY B. MALLORY: One specific gravity was 1.022, and the others ranged from 1.010 to 1.015. Someone put down a question mark against the 1.022 figure, however.

DR BAUER: I shall assume that the specific gravity of 1.015 represented the ability of the kidneys to concentrate.

Was there any increase in cells in the spinal fluid? Was the spinal-fluid protein increased?

DR MALLORY: The protein is recorded as 38 mg per 100 cc by the electrophoretic method and 42 by the old method.

DR BAUER: There was no mention of cells?

DR MALLORY: Yes, I see a note saying that there were 3 cells per cubic millimeter.

DR BAUER: Are there any x-ray films of the knee?

DR STANLEY M. WYMAN: No. The chest films show an apparently normal upper lung. The heart shadow is increased in transverse diameter, with prominence of the apical portion, probably representing an enlarged left ventricle. The aorta is prominent in the ascending portion and shows a suggestion of bulging but no calcification in this portion of the aorta or elsewhere in its thoracic course.

DR BAUER: Would you care to say anything further about the aortitis?

DR WYMAN: It certainly is suggestive of aortitis. Examination of the stomach shows a crater on the lesser curvature at the angle. An additional finding not noted in the original record is a deformed duodenal cap, which although present, is not well

demonstrated in this film. There is a suggestion of a filling defect in the prepyloric region, which is better seen at the examination done seventeen days later.

DR BAUER: A prepyloric crater as well as one on the lesser curvature?

DR WYMAN: It is suggestive.

DR BAUER: Nothing is said about that in the abstract.

DR WYMAN: No. These spot films show the decrease in size of the crater on the lesser curvature. The next two films selected from the pvelogram examination are not satisfactory for fine detail, but they show excretion of dye in fairly good concentration without gross distortion or dilatation.

DR BAUER: Would you say that the patient excreted the normal amount of dye?

DR WYMAN: I think he did well for a man of seventy-five.

DR BAUER: With a specific gravity of 1.015?

DR WYMAN: Very well indeed.

The film of the skull shows no demonstrable bone disease. These films of the long bones, the lower legs and forearms reveal no definite bone destruction. The joint spaces, the wrists and the ankles appear essentially normal.

DR BAUER: The question is, How many diagnoses should one make? Can all the findings be explained on the basis of one disease? I do not believe so. I think there can be no doubt that this man had multiple myeloma. The evidence for that is clear-cut and certainly adequate. It is reported that the electrophoretic studies failed to reveal Bence-Jones protein in the serum. This, however, has been true of other cases of multiple myeloma. Likewise, a hyperproteinemia and a hyperglobulinemia are not always present.* I think that this man probably had a complication seen in multiple myeloma—namely, amyloidosis. There are, of course, three kinds of amyloidosis: primary amyloidosis, amyloidosis associated with multiple myeloma and secondary amyloidosis. Visceral involvement is much less frequent in the first two, and the staining reactions for amyloid are variable and atypical. It is also of interest that in most cases of primary amyloidosis in which the total serum proteins have been determined they have been found to be essentially normal.* In amyloidosis associated with multiple myeloma Bence-Jones proteinuria is present in only about half the cases. To establish the exact incidence of primary amyloidosis one must suspect and if possible rule out myeloma in all cases of amyloidosis in which no obvious cause is found.

This man had a positive blood Hinton test, spinal-fluid abnormalities, enlargement of the left ventricle, evidence of aortic-valve incompetence and enlargement of the ascending portion of the aorta. Therefore, I would like to make the additional

*Done by the Howe technique.

CASE 35142

PRESENTATION OF CASE

A seventy-five-year-old Portuguese laborer was admitted to the hospital because of epigastric pain, anorexia and loss of weight

The patient had quit work one year before entry because of weakness, but stated that he had been well up until about two months before admission. His weight had fallen from 154 to 127 pounds. At the same time he had painful, swollen knees, but this complaint had disappeared. Three or four weeks before admission he began to experience intermittent, nonradiating, "burning" pain in the middle and left epigastrium, which occurred half an hour to one hour after meals. The pain was very sharp for ten or fifteen minutes and then wore off. Occasionally, the pain reappeared between meals. Milk and food seemed to relieve it for a while, as did belching. Sometimes he vomited a small amount with relief. There were no changes in bowel habit, and he did not notice the color of the stool. There was no hemoptysis. There was no jaundice, distention, dysphagia or prominent genitourinary symptoms. There had been recent mild ankle edema. A physician had given him pills and a white liquid for the pain, but these gave no relief. Diet during the present illness had consisted of tea, toast, soups and juices.

About twenty-five years before entry he had suffered episodes of epigastric pain, which he could not clearly describe. He continued to work, and eventually these wore off without medication. Several years later he underwent an appendectomy. He denied the symptoms or treatment for syphilis or gonorrhea.

Physical examination revealed a pleasant, elderly man, showing signs of weight loss. There was no jaundice. There was a cataract in the left eye. There were a few, shotty, firm lymph nodes in the axillas, especially on the right. There were prominent inguinal chains bilaterally. The lungs were clear. The heart was boot-shaped, with the point of maximal impulse at about the midclavicular line. There were occasional premature beats, and the aortic second sound was greater than the pulmonary. There was a Grade I, blowing diastolic murmur loudest in the aortic area, a Grade I whine in diastole along the upper left sternal border, and a Grade II systolic murmur heard loudest at the apex but also heard in the axilla and at the base. The abdomen was flat, with normal peristalsis. There was an appendectomy scar in the right lower quadrant. There were no palpable masses or tenderness. The liver edge was palpated one fingerbreadth below the right costal margin on inspiration and was prominent across the epigastrium. There was a + ankle edema.

The temperature was 99°F, the pulse 96, and the respirations 18. The blood pressure was 146 systolic, 70 diastolic.

The urine had a specific gravity of 1.015 and gave a +++ test for albumin, and the sediment contained a few white cells and a rare hyaline cast. Examination of the blood disclosed a red-cell count of 2,570,000, with a hemoglobin of 7.5 gm, and a white-cell count of 17,000, with 27 per cent neutrophils, 67 per cent large lymphocytes and 4 per cent monocytes. Anisocytosis and hypochromia were noted. The stools gave a ++ guaiac reaction. The blood Hinton test was positive. The serum protein was 6.20 gm per 100 cc, with an albumin of 3.86 and a globulin of 2.34 gm (albumin-globulin ratio of 1.7). The nonprotein nitrogen was 27 mg, phosphorus 3.7 mg, and alkaline phosphatase 3.5 units per 100 cc. The prothrombin time was 24 seconds (normal, 16 seconds), the cephalin flocculation test was negative in twenty-four and forty-eight hours. A gastric aspiration showed free hydrochloric acid.

The patient's condition remained essentially unchanged. A gastrointestinal series revealed a grossly benign ulcer crater, 1.5 cm in diameter, approximately 1 cm beyond the lesser curvature of the stomach. A roentgenogram of the chest showed a heart enlarged in the region of the left ventricle. The aorta was somewhat widened, particularly in the ascending portion. On the fourth hospital day urine gave a ++++ test for albumin, and the sediment contained many red cells, with an occasional white cell and hyaline cast. A blood smear showed 8 per cent plasma cells, and a subsequent sternal-bone-marrow aspiration disclosed a marked diminution of myelopoiesis and erythropoiesis. About 80 per cent of the cells were mature plasma cells, with a few blast forms and binucleated plasma cells. Bence-Jones protein was found to be abundant in the urine. Roentgenograms of the skull, forearms, wrists and hands showed no evidence of bony disease. On intravenous pyelogram the kidneys excreted the dye promptly and outlined nondilated calyces, pelves and ureters. A serum protein electrophoretic separation produced a normal pattern, indicating the absence of Bence-Jones protein in the serum. The spinal-fluid gold-sol curve was 0000344211. A urine culture showed colon bacilli and a few nonhemolytic streptococci. On the eleventh hospital day the patient stated that he no longer had epigastric pain but that he did feel weak "all over." Five days later the white-cell count was 47,800, with 22 per cent neutrophils, 44 per cent large lymphocytes and 34 per cent small plasma cells. On the nineteenth hospital day a gastrointestinal series showed that the gastric ulcer had decreased considerably in size. The stools became black and gave a ++++ guaiac reaction. The blood calcium was 10.6 mg, phosphorus 9.2 mg, phosphatase 3 units, nonprotein nitrogen

et al² They observed 4 cases with normal total serum protein levels with hyperglobulinemia, 11 cases with apparently normal distribution of serum protein fractions and 1 with marked hypoproteinemia (40 and 35 gm total serum protein levels) It is also of interest that the Congo-red test is more often negative than positive in cases of primary amyloidosis and amyloidosis associated with multiple myeloma

DR WALTER F LEVER I did the electrophoretic analysis The albumin was 51 per cent, which is a value well within normal limits With the electrophoretic analysis normal albumin is 55 per cent

DR KRANES I think it is of interest that this man had a normal renal function until he had a sudden change

DR BAUER I overlooked this point I thought the nonprotein nitrogen was 150 mg per 100 cc before the hemorrhage

DR KRANES Before or after?

DR LEVER The nonprotein nitrogen rose first

DR KRANES I get the impression that the nonprotein nitrogen rose following the hemorrhage

DR BAUER Yes, on rereading the case history I find that is right I still think this patient had amyloidosis of the kidneys However, Dr Kranes is right about the sequence of events before and after the hemorrhage The hemorrhage was "the straw that broke the camel's back" and caused the renal ischemia that resulted in the rapid rise in the nonprotein nitrogen

CLINICAL DIAGNOSES

Plasma-cell myeloma

Uremia

Duodenal ulcer

DR BAUER'S DIAGNOSES

Multiple myeloma

Amyloidosis, associated with multiple myeloma

Tertiary syphilis

Syphilitic aortitis

Inactive central-nervous-system syphilis

Duodenal ulcer, healed

ANATOMICAL DIAGNOSES

Multiple myeloma, plasmocytic

Myeloma kidney

Retroperitoneal hematoma

Syphilitic aortitis

Benign ulcer of stomach

PATHOLOGICAL DISCUSSION

DR MALLORY Autopsy showed very characteristic multiple myeloma involving the marrow of all bones examined—the vertebra, ribs and sternum The plasma cells, as Dr Jacobson noted, were quite mature in type, although in the marrow tumors multinucleated cells are quite common It is rather unusual in cases of plasma-cell myeloma to see

many plasma cells in any of the viscera outside the bone None were found in this case Going back to the other features of the autopsy, there was an active peptic ulcer of the stomach, and there were two diverticula of the duodenum but no ulcers We did not find any evidence of amyloid disease The heart was normal except for a slight thickening of the aortic cusps The ascending aorta was diffusely dilated, and it was very difficult to decide whether this was arteriosclerotic or syphilitic I think it probably was burnt out and very inactive syphilitic aortitis The kidneys were a little large, weighing 410 gm, and showed the characteristic picture seen in Bence-Jones proteinuria The tubules were filled with casts and precipitated protein In a few cases foreign-body giant cells were noted around the casts, which is rather specific for the so-called myeloma kidney

We did not have permission to examine the central nervous system so that I cannot say whether or not there was evidence of syphilis there

DR BAUER No evidence of amyloid?

DR MALLORY No

DR BAUER And it was looked for?

DR MALLORY Yes—in significant amounts it could not be missed by any method

DR BAUER Some people disagree it may not be demonstrable in primary amyloid disease and in the type associated with multiple myeloma The Congo red may not be absorbed

DR MALLORY Yes, but one sees hyaline-like tissues whether or not it stains correctly with the method One can miss an isolated deposit of amyloid, for instance, one limited to the joints, in cases in which the extremities are not dissected, but generalized amyloidosis could not be missed if routine microscopical examination was done

DR BAUER So you would not miss it in the kidney?

DR MALLORY No

One other finding concerns the point that Dr Kranes made there was evidence of extensive hemorrhage within the body,—the retroperitoneal tissues, particularly around the pelvis, and the lymphoid tissues, were filled with old hemorrhage, much of which had coagulated, and was dark brown It must have been present many days before death So there was internal as well as external hemorrhage, which may have had something to do with the development of the renal insufficiency The purpuric tendency could have been due to renal insufficiency or to bone-marrow replacement in this case

REFERENCES

- 1 Case Records of the Massachusetts General Hospital (Case 35141) *New Eng J Med*, 240:572-577, 1949
- 2 Gutman A B, et al Fractionation of serum proteins in hyperproteinemia, with special reference to multiple myeloma. *J Clin Investigation* 20:765-783 1941
- 3 Eisen H N Primary systemic amyloidosis. *Am J Med*, 1:144-160 1946

diagnoses of tertiary syphilis and syphilitic heart disease with aortitis. I well appreciate that in some cases of primary amyloidosis and the form associated with myeloma, endocardial and valvular amyloid deposits do occur.

There are a number of questions one would like to answer. Were the joint symptoms a year before entry due to the multiple myeloma or the associated amyloidosis? In some cases of primary amyloidosis and the type associated with multiple myeloma large deposits of amyloid are found in the articular tissues. Such patients may have joint pain and swelling, and the amyloid deposits may be demonstrable on x-ray examination. Unfortunately, no x-ray films of the joints were taken, however, it seems fair to assume that they would have been normal and that there was no clear-cut evidence of skeletal involvement in this case. The other question to be answered is: Did this man have a duodenal ulcer as well as a gastric ulcer? (I did not realize this possibility until I saw the x-ray films.) We know that involvement of the gastrointestinal tract occurs in amyloidosis and that gastric ulcerations do take place. Should one explain the gastric lesions on the basis of the associated amyloid disease, or should one make a diagnosis of a benign gastric ulcer as suggested by Dr. Wyman? I must say that I prefer to "stick my neck out," and consider the gastric lesion as being part and parcel of the amyloidosis. Primary amyloidosis and the type associated with multiple myeloma may be characterized by diffuse vascular involvement. This was demonstrated in the case I was tripped on about a year ago¹ (I made the diagnosis of Osler's erythema group of skin diseases with visceral involvement). Such cases may show marked deposition of amyloid in the media, sometimes with complete replacement thereof. In such cases one observes cutaneous manifestations, subcutaneous amyloid deposits and recurring purpura or purpura due to very slight trauma. In this case the bleeding occurred from all orifices. Of course, the patient may have bled from the gastric ulcer or the old duodenal ulcer, which Dr. Wyman thinks may have become activated.

As I said before, I think this patient had multiple myeloma with associated amyloid disease, amyloid deposition in the gastrointestinal tract, particularly the stomach, with associated ulcerations. As a rule the last are rather superficial. I doubt the presence of skeletal amyloidosis. The other diagnoses are syphilitic heart disease, syphilitic aortitis and a healed duodenal ulcer. I shall include also central-nervous-system syphilis because of the marginal spinal-fluid protein value and the abnormal colloidal gold curve—findings that indicate relatively quiescent or inactive central-nervous-system syphilis.

The apparently normal distribution of serum protein fractions (albumin of 5.06 gm and globulin of 2.05 per 100 cc) has been reported by others.²

The results obtained by the Howe technic and the electrophoretic method are not always comparable, as shown by Gutman et al.² The same investigators concluded that unless special precautions are taken, the Howe method (which gives high values for albumin in normal serum) occasionally gives much too high values for serum albumin in multiple myeloma, the error being due to the abnormal protein component in the 21.5 per cent sodium sulfate filtrate of some myelomatous serums.

DR ALFRED KRANES: Do you want to say anything about the kidneys?

DR BAUER: I meant to and forgot. I think the urinary abnormalities were due to amyloidosis. Marked albuminuria, hematuria (usually of a lesser degree than in this case) and pyuria have been noted in some cases of amyloidosis associated with multiple myeloma. Of course, there is always the possibility that the Bence-Jones protein precipitates out in the renal tubules. About a third of the cases of amyloidosis associated with multiple myeloma have renal involvement. Histologic examination of the kidneys shows amyloid in the glomeruli and in the media of vessels. I predict that the kidneys will show amyloid.

DR DANIEL S. ELLIS: Do you have to presuppose that amyloid deposits and not the myeloma itself caused this picture?

DR BAUER: No, but I think I am dealing with a disease akin to primary amyloidosis. I appreciate that in the case of a patient of seventy-five it is hazardous to explain so many findings on the basis of one disease. However, I prefer to do so, even though the chance of being wrong is great.

DR BERNARD M. JACOBSON: I would like to take issue with Dr. Bauer on a few items. I would not pass off the normal globulin so easily. I think it is a clinical finding against myeloma. On a statistical basis this is only the third case in this hospital with normal globulin by the Howe method.

DR BAUER: Have you read the article by Gutman et al.²

DR JACOBSON: No, I will. But I will not retract the statement. In the second place, these plasma cells as I saw them in the blood smear and bone marrow were extremely mature, quite different from the ordinary case of myeloma. One might wonder because some writers say that this maturity indicates a better prognosis than the immature cells. Obviously, that did not apply here. Hematuria and pyuria cannot be called common findings in amyloid disease.

DR BAUER: Nevertheless it is recorded in 2 cases. I reviewed.

DR JACOBSON: In this article?

DR BAUER: No, 2 cases reported by Eisen.¹

DR JACOBSON: That may be true, but it is not common in this hospital.

DR BAUER: Serum protein fractions in multiple myeloma are reported in some detail by Gutman.

ued prosperity is dependent on its readers and its advertisers, and may the twain frequently meet! Suggestions for bringing about, continuing and strengthening this happy union and for improvements in advertising readability will be welcomed. It goes without saying that efforts are constantly made to ensure advertising material only of the highest grade.

STREPTOMYCIN AS A PROPHYLACTIC AGENT

Soon after the discovery of streptomycin it was shown that this antibiotic is highly active against the gram-negative bacilli and against many of the other organisms that constitute the flora of the large bowel. It was also demonstrated that streptomycin given by mouth is poorly absorbed so that about 95 per cent of an orally administered dose could be recovered in the feces and only about 2 per cent in the urine.

Direct studies in experimental animals have shown that streptomycin is highly effective in reducing the total number of bacteria in the feces and that this reduction can be accomplished more rapidly and more thoroughly with streptomycin than with other available agents, particularly the sulfonamides. Some of the early studies in animals¹ and in man² gave no indication of the development of resistance by the fecal organisms. Subsequent investigations,^{3, 4} however, have indicated that there is a rapid replacement of the fecal organisms by streptomycin-resistant organisms. This tendency was less marked when the so-called enteric sulfonamide drugs, such as sulfasuxidine and sulfathaladine, were used in conjunction with streptomycin, but even the combination of such agents failed to prevent the appearance of the resistant strains.

The studies of Poth and his associates⁵ have demonstrated the value of sulfasuxidine in the preoperative and postoperative care in surgical procedures on the bowel. In their animal experiments they also showed that open technics of anastomosis could more safely be utilized if adequate doses of sulfasuxidine were used. Streptomycin administered orally failed to maintain an alteration of the bacterial flora for a sufficient time to permit

the experimental evaluation of its effects on the healing of the bowel wound. When both sulfasuxidine and streptomycin were used, the results were essentially the same as when sulfasuxidine alone was used. The use of streptomycin alone had to be abandoned after the first few experiments because the immediate reduction in the bacterial count was not maintained.

Rowe and his co-workers⁴ have studied the fecal flora of patients before and after operations on the large bowel and attempted to determine the value of sulfathaladine and streptomycin as adjuncts to this type of surgery. They found that the fecal coliform organisms could be reduced 99.99 per cent in an average of three and a half days when the patient was given sulfathaladine in doses of 0.1 gm per kilogram of body weight per day in divided doses. With the oral administration of streptomycin in doses of 2 gm per day a similar reduction was accomplished in twenty-four hours. Reversion of bacterial counts due to resistant organisms was not observed with the sulfonamide but did occur with streptomycin, particularly when a dose of only 0.5 gm per day was used. The combination of the two drugs even in the larger doses did not entirely prevent this reversion. In the course of their studies Rowe and his associates observed a case in which a coliform organism became resistant to both drugs during the preoperative prophylactic treatment and was later responsible for a postoperative peritonitis. The infection proved fatal, since it obviously could not be affected by these chemotherapeutic agents.

On the basis of their preliminary observations these authors suggest that streptomycin should not be employed alone but that a preliminary test of sulfathaladine for five to seven days and streptomycin for about forty-eight hours or less is worthy of a trial. Actually, the data suggest that the combination used for no more than twenty-four hours is the best regime in preparation of the bowel for surgery. They emphasize the fact that prolonged administration of streptomycin is not desirable and that it is unlikely that the combination of the sulfonamides with streptomycin can alter the total bacterial counts for any prolonged periods.

More recently Lockwood and his co-workers,⁵ after noting the conflicting reports in the literature,

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TEAMWORK

ANY undertaking prospers according to the quality of effort that goes into its various activities. The physician who practices his profession must be well grounded in its fundamental principles and skilled in their application. He must constantly add to his knowledge and, with the equipment thus assured, he must employ also his personality in gaining the confidence and the respect of his patients. He must be faithful, diligent, cheerful and self-sacrificing, and he must have also the co-operation of those with whom he labors.

The success of an industry depends primarily on the quality of its product. To ensure this quality, however, there must be comparable quality in the raw materials used and there must be skill and integrity in the workmanship. In order that the enter-

prise shall succeed there must be attractive but honest advertising, backed up by good salesmanship. The confidence of the consumer must be obtained and secured.

So it is with journalism, and even with medical journalism, for this professional activity must operate under the same economic laws that apply to the practice of a profession or the operation of a trade. If continuing success is to be enjoyed, the quality of the product must be maintained at a high level as the basic factor. This quality must also constantly be brought to the attention of new readers and possible subscribers, for with publications as with other living matter, a strong circulation is an essential of health.

Not only does the circulation itself bring to the journalistic tissues those corpuscular bodies known to the creditor class as hard cash, it implies also that element of readability with which all but the most pessimistic of advertisers are visibly impressed.

The lesson is obvious. Those who have products to sell will display their wares where they will be favorably noticed by the greatest number of prospective buyers.

Two complementary factors are necessary if the experiment in teamwork is to achieve its best results. The sellers must present their products, which must conform to the highest ethical standards, as attractively and as arrestingly as possible and the readers on their part must bear in mind that the advertising pages of a journal may prove just as valuable to them as its text, and that by reading the advertisements and mentioning the journal when they buy or make inquiries they are strengthening the confidence of the advertiser in the medium that he has selected.

The *New England Journal of Medicine* having just passed its one hundred and twenty-first birthday—its one hundred and thirty-seventh according to a more favorable way of reckoning—is doing very well in both particulars and is enjoying, in these critical years, its peak circulation as well as its highest advertising revenue to date. These increases, however, are barely sufficient to neutralize rising costs of publication and the *Journal* is not at all unmindful of the fact that its contin-

workers have alleviated thousands of desperate social situations by making modern treatment available. Its educational program has brought the word cancer out into the public eye and brought more and more early curable patients to the doctors' offices.

From the standpoint of the physician all this adds up to the fact that it is an organization whose every effort helps correct the kind of situation that leads unthinking people to clamor for Government medicine. If for no other reason than his interest in humanity as a whole, the thoughtful doctor will support this society by working for it or with it and by contributing to its drive. He will show the people that he appreciates what they are doing by giving generously himself and by asking his patients to give.

If any prospective contributor does not know his local treasurer or the address of his state headquarters, he may merely put his check in an envelope marked "Cancer, c/o Local Postmaster." This letter will go to his state headquarters.

DOCTOR NEEDED

ONE of the outstanding needs in the distribution of medical care is that of the rural district. This need is recognized in the pediatric survey recently conducted by the American Academy of Pediatrics, and in the creation of a committee on rural medical service by the American Medical Association in 1945. It is recognized in the controversial ten-year program of the federal security administrator.

Efforts are being directed toward the solution of this problem, not only by the agencies mentioned but by others, such as the Board of Missions of the Methodist Church that is currently trying to provide medical care for many rural areas. Outstanding among these medically needy communities, according to the Methodist Board of Missions and Church Extension, of 150 Fifth Avenue, New York, is Newton County, in northwest rural Arkansas. Here 10,000 persons are without a physician or a nurse and the nearest hospital is twenty-five miles from the county seat.

NOTES FROM THE MEDICAL EXAMINER

ASPHYXIATION FOLLOWING THERMAL BURNS OF THE FACE

Persons trapped in conflagrations may die as a result of damage to the respiratory tract without injury to the surface of the body.¹ The problem of whether smoke and irritant gases or tremendously heated air is the responsible agent has often been discussed.² In 1945 Moritz, Henriques and McLean³ reported an experimental study of the effects of inhaled heat, which showed that only when the original temperature of heated air is high enough to produce instantaneous burning of the skin and upper respiratory mucosa is there thermal damage to the pulmonary parenchyma. The amount of heat contained in the small volume of tidal air is the limiting factor for thermal injury of the air passages, whereas skin lying on the surface of the body is exposed to relatively enormous volumes of heated air passing across it by convection currents. For this reason it is safe to conclude that no damage to the respiratory tract *due to heat alone* can occur without burns of the face. Conversely, in the presence of burns of the face, there may be injury of the air passages.

Two of the 3 patients in the following case reports would probably have survived their burns had the attending physicians appreciated the hazard of respiratory obstruction coincident with burns of the face.

CASE 1 A 40-year-old man was removed from a conflagration in an abandoned dwelling at 5:30 a.m. In the building there were "500 cases of Sterno," the residue of numerous alcoholic sprees. Pressure dressings were applied to second-degree and third-degree burns of the face and hands, and to spotty areas of the shoulders and arms. The blood pressure was 120/70, and the pulse 100. Intravenous injections of glucose in saline solution were given. He drank milk frequently and talked easily, stating that he felt well. At 2:00 p.m. he was observed to be suddenly breathing with difficulty. Aspiration, artificial respiration and intracardiac adrenalin were ineffective, and death occurred at 2:15 p.m., 83½ hours after removal from the fire.

Post-mortem examination revealed the body of a well developed and well nourished man, 63½ inches in length, weighing 145 lb. The hair of the head was uniform, wavy. There was second-degree and third-degree burning of the face, left shoulder and hand, right axilla, upper arm, forearm and hand. The total burned area was less than 10 per cent. Significant autopsy findings were fluidity of blood, edema and hyperemia of the lungs, the left weighing 360 gm. and the right 460 gm., extensive deposition of carbonaceous material throughout the trachea and bronchial tree, and laryngeal edema most marked at the glottis, reducing the laryngeal diameter of about 0.3 inch.

In this case the burns were of slight extent, the face severe. The carbonaceous material in the trachea and bronchi is proof that the products of combustion were inspired.

CASE 2 A 40-year-old man was removed from a conflagration in an abandoned dwelling at 5:30 a.m. In the building there were "500 cases of Sterno," the residue of numerous alcoholic sprees. Pressure dressings were applied to second-degree and third-degree burns of the face and hands, and to spotty areas of the shoulders and arms. The blood pressure was 120/70, and the pulse 100. Intravenous injections of glucose in saline solution were given. He drank milk frequently and talked easily, stating that he felt well. At 2:00 p.m. he was observed to be suddenly breathing with difficulty. Aspiration, artificial respiration and intracardiac adrenalin were ineffective, and death occurred at 2:15 p.m., 83½ hours after removal from the fire.

recorded their own appraisal of orally administered streptomycin as an intestinal antiseptic. They did careful serial quantitative bacterial counts in the feces of patients receiving streptomycin by mouth. Only half the patients showed a drop in the number of coliform organisms, and this drop was prolonged and significant in only a fourth of the cases. There was no significant reduction in the number of streptococci in 87.7 per cent of the cases, and 38.9 per cent failed to show any reduction in the clostridial counts in the feces. The bacilli demonstrated rapid development of resistance to streptomycin so that many became able to proliferate in the concentration of streptomycin present in the feces. The results in a small group of cases treated with streptomycin and sulfathaladine were also inconsistent. These workers concluded that streptomycin administered by mouth is unpredictable and unreliable, and its use in preoperative preparation of surgical cases is not recommended.

It is also noteworthy that streptomycin-resistant organisms may appear in the feces of patients who receive streptomycin only by intramuscular injection.⁶ This finding is not surprising since it has been shown that streptomycin-resistant organisms also appear in the throat cultures of 98 per cent of patients who have been under treatment with intramuscular injections of streptomycin for several days.⁷

In general, some of the properties of streptomycin—namely, its tendency to produce serious vestibular damage on prolonged use and particularly the rapid replacement of the bacterial flora by highly resistant strains—suggest that it is a very poor prophylactic agent in the usual sense. It may, however, be useful under certain circumstances provided it is given under optimal conditions. The data cited suggest that in cases of the usual gram-negative bacillary infections, such as might arise during large-bowel surgery or during manipulations of an infected urinary tract, streptomycin administered for not more than twenty-four hours prior to the operation may reduce the volume of infection at the operative site and thus diminish the chances of postoperative infection and thereby improve the healing process. If the bowel is to be opened a sulfonamide may be used for the same or a longer period preoperatively.

In cases of tuberculosis in which the organisms multiply more slowly and resistant strains may not appear in large numbers until after two or three weeks of streptomycin treatment, preliminary administration may be carried out for about a week before extensive operations on tuberculous lesions and still permit two weeks or more of treatment postoperatively with the expectation that the streptomycin effect will be sustained during this period. The longer the period of preoperative streptomycin treatment, the greater the risk of an increased number of resistant tubercle bacilli and the less the opportunity for the streptomycin effectively to cope with any postoperative spread of the tuberculous infection.

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THE AMERICAN CANCER SOCIETY

DURING the last few years the American Cancer Society has raised and spent many millions of dollars on research, service and education. Positive accomplishments of its work may be found in all parts of the country. At the same time doctors, hospitals, federal, state and local government units, and individuals have accomplished much in this field. The local units of the Cancer Society in every city and town are now asking the people for more money. In view of the large efforts of the doctors, the Government and other organizations and individuals is this money needed?

The answer must be that it is. This organization is the best possible catalyst to stimulate and pull together the efforts of everybody. It is set up so that it is a true partnership of doctors and the people in this common effort.

Its research program has already affected the treatment of many kinds of cancer. Its devoted

CORRESPONDENCE

REPUDIATION OF AMERICAN MEDICAL ASSOCIATION ASSESSMENT

To the Editor I delayed paying the \$25 00 assessment of the American Medical Association until there was time for a statement of policy authorized by the Association Now that this has appeared, I have decided not to pay the assessment of \$25 00 to support the policy of the American Medical Association because that statement as set forth in the February 19 issue of the *Journal of the American Medical Association* is too vague to be satisfactory, particularly as to legislation to provide the money to carry out its various items, and because the official answer of the American Medical Association to a group of protestants, who, to those familiar with American medicine, represent the cream of the profession, is unsatisfactory, since it does little more than call names and does not acknowledge the seriousness of the situation that called out this protest and does not indicate any intention of attempting to correct it.

This determination of mine not to pay the assessment is a protest against the present policy of the American Medical Association, not a support of governmental compulsory insurance to provide medical care along the lines proposed by President Truman, that I believe to be highly undesirable

HENRY A CHRISTIAN, M D

Brookline, Massachusetts

NOTE Over 2300 fellows of the Massachusetts Medical Society have already made their contribution to the American Medical Association — Ed

FURTHER COMMENT ON EXTRARENAL AZOTEMIA

To the Editor In the January 20 issue of the *Journal*, Appel and Townsend reported on an interesting case of "Extrarenal Azotemia" with recovery No mention was made of the possibility of carbon tetrachloride poisoning The possibility of carbon tetrachloride poisoning as a cause of uremia is frequently overlooked The liver damage in this poisoning may be transient, and jaundice may be absent. It may be difficult to elicit a history of exposure to carbon tetrachloride because of the uncertain interval between exposure and renal shutdown The differential diagnosis of any unexplained uremia should include the possibility of carbon tetrachloride nephrosis

JACOB J SILVERMAN, M D

Staten Island, New York

A CLINICAL SUGGESTION

To the Editor Skin-temperature determinations are frequently of considerable clinical value The available methods vary from the application of the observer's hand to the use of electrothermometers such as the "dermatherm" and "dermalor"

With increasing interest in the study and treatment of diseases of the peripheral vascular and sympathetic nervous systems, I should like to suggest an instrument that is simple, inexpensive and adequately accurate for ordinary testing It is an English skin thermometer Its chief differences from the ordinary clinical thermometer are that the glass of the mercury-containing bulb is much thinner and that there is no trap, and therefore no shaking is necessary between readings

It has been found precise to within 1°F when checked against the electric apparatus in the Hypertension Laboratory of the Massachusetts General Hospital (by Dr Davitt Felder) Attention was called to this thermometer by Dr Moses Suzman, of Johannesburg, in 1947 I have found none like it manufactured in this country Anyone who is interested may procure these instruments in 4-inch or 8-inch sizes from L H Marks, Ltd, 1 Belfast Road, London, N 16

JOHN B SEARS, M D

416 Marlborough Street
Boston

FAMILY DOCTORS NEEDED

To the Editor Dr Henry F Howe's letter in the March 10 issue of the *Journal* should be sent to the dean and professors of medicine of every medical school in the United States If the A M A would expend some of its so-called educational-fund assessment on the dissemination of this sort of plain common sense there would be far less chance of the public's demanding or even accepting socialized medicine

At present the medical schools and large hospitals are engaged in turning out specialists with no regard for the necessity of general practitioners Here in my own community, within twenty miles of Boston and access to all its facilities, with an increase of over 500 families in the last five years and the loss by death of two physicians, there has been no addition of qualified family physicians

During this period I have had numerous young surgeons and other specialists inquire about the chance of establishing a lucrative practice Not a single man has evinced the slightest interest in helping to carry the daily load of calls, which neither demand nor can afford a specialist There is not even the excuse of lack of housing, since a most desirable house with adequate office arrangement is available

The few general practitioners in Natick are exhausting themselves trying to provide medical coverage for the population With long waits for both office and house calls it is no wonder that the public is becoming dissatisfied with the medical profession's handling of the situation A serious epidemic would be a disaster

I believe that many young medical students would gladly devote themselves to general practice, with its comparatively earlier financial returns, if the role of family physician were not looked down upon in the medical schools

A medical profession that does not provide what the public needs or wants will have only itself to blame if the public turns to Government medicine to fill this lack

JAMES E VANCE, M D

Natick, Massachusetts

NOTICES

BOSTON CITY HOSPITAL HOUSE OFFICERS ASSOCIATION

The following programs of the Boston City Hospital House Officers Association will be presented in the Evening Lecture Series

- April 11 The Surgical Problem of Carcinoma of the Female Genitalia Persistent or Recurrent after Conservative Treatment. Alexander Brunschwig, M D, attending surgeon, Memorial Hospital for Treatment of Cancer and Allied Diseases, and professor of clinical surgery, Cornell University Medical College
- April 12 Role of Iron Metabolism in Hypochromic Anemia Carl V Moore, M D, associate professor of Medicine, Washington University School of Medicine, St. Louis
- April 14 Lower-Nephron Nephrosis Baldwin Lucké, M D, professor of pathology, University of Pennsylvania School of Medicine.

These programs are held at 7-00 p m in the New Cheever Amphitheater of the Dowling Building, Boston City Hospital All interested persons are invited to attend

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the Lower Out-Patient Department Amphitheater, Massachusetts General Hospital, on Tuesday, April 12, at 8 p m

PROGRAM

- Anatomy and Physiology of Splanchnic Pathways from the Viscera Dr James C White
 - Anatomy and Physiology of Pain Pathways in the Brain Stem and Spinal Cord Dr William H Sweet.
- A subsequent meeting will be held on May 10

sisted of demerol and penicillin at 3-hour intervals. He was said to show marked hemoconcentration and died at 7 39 p m — 19 hours after injury.

Post-mortem examination disclosed the body of a well developed and well nourished man, 71 inches in length, weighing 165 lb. The hair was extensively burned away. There was burning of the scalp, entire face, anterior portion of the neck, shoulders and both hands. The total area was 10 per cent of body surface. Severe edema of the face, scalp and neck was present. A pressure dressing had been applied to the head and shoulders with firm gauze binding crossing diagonally from head to axilla over the throat. The trachea and bronchi showed no gross injury. The right lung weighed 460 and the left 300 gm. Both lungs were crepitant throughout. Surrounding the lower pharynx and larynx there was massive edema. The glottis was almost occluded by submucosal edema.

This case demonstrates the additional obstructing force of edema extrinsic to the pharynx and larynx.

CASE 3 A 43-year-old Negro was removed from a conflagration resulting from a defective oil heater. He was admitted to the hospital at 7 30 a m, extensively burned but alert and oriented. Pressure dressings were applied. Shortly before death at 4 15 p m, alert attendants observed respiratory distress, and an emergency tracheotomy was performed but without benefit.

Post-mortem examination showed the body of a Negro 68 inches in length, with second-degree and third-degree burns of the right forehead and cheek, eyelids, lips, chin and anterior portion of the neck, with additional burns totaling about 70 per cent of the body surface. There was a tracheotomy tube passing down through a region of massive edema of the pretracheal tissues into the trachea. Surrounding the inner orifice of the tube was a pool of clotted and liquid blood obstructing both tube and trachea. Massive edema was present throughout the neck, and there was a moderate degree of glottic edema.

The interval of twenty-eight hours prior to autopsy reasonably explains the dissipation of edema fluid from the submucosal glottic tissues. The extraordinary degree of peritracheal and subcutaneous edema interfered with insertion of the tracheotomy tube and accounts for the hemorrhage from the incision funneling into the trachea.

In these cases, glottic edema precipitated asphyxiation. Whether an appreciable part of the edema was due to heat is debatable, but the burns of the face indicate close contact with the concentrated irritant gaseous products of combustion.⁴ Intubation and prophylactic tracheotomy are possible preventive measures, probably even superior to competent nursing care for thirty-six hours after injury.

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RICHARD FORD, M D

Research Fellow in Pathology and Legal Medicine,
Harvard Medical School, and Associate Medical
Examiner, Suffolk County

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR FEBRUARY, 1949

RÉSUMÉ

DISEASE	FEBRUARY 1949	FEBRUARY 1948	SEVEN-YEAR MEDIAN
Chancroid	8	4	2*
Chicken pox	3776	1838	1651
Diphtheria	33	19	19
Dog bite	680	600	511
Dysentery bacillary	0	11	9
German measles	206	79	188
Gonorrhea	203	186	345
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	0	2	2*
Malaria	0	3	8
Measles	5285	2093	1877
Meningitis meningococcal	4	9	19
Meningitis Pfeiffer bacillus	3	2	2
Meningitis, pneumococcal	2	2	4
Meningitis staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis undetermined	3	5	5
Mumps	1302	1559	1113
Polio myelitis	0	2	1
Salmonellosis	2	4	4
Scarlet fever	1312	429	1201
Syphilis	168	198	363
Tuberculosis pulmonary	188	200	200
Tuberculosis other forms	10	10	14
Typhoid fever	4	1	2
Undulant fever	2	5	1
Whooping cough	249	294	595

*Five year median

COMMENT

Diseases above the seven-year median were chancroid, chicken pox, diphtheria, dog bite, German measles, measles, mumps, scarlet fever and typhoid fever.

Diseases below the seven-year median were bacillary dysentery, poliomyelitis, salmonellosis and whooping cough.

Scarlet fever rises and falls in fairly predictable cycles over the years of reporting. The low year of such a cycle was 1947. In 1948 there was a reversal of the trend, and the disease can be expected to rise to another peak during the next year or two. The incidence of measles was the highest for February since 1935. That for chicken pox was the highest since reporting began in Massachusetts. The incidence of diphtheria remained high.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Anthrax was reported from Peabody, 1, total, 1.

Diphtheria was reported from Billerica, 2, Boston, 19, Chelsea, 1, East Brookfield, 3, Everett, 2, Malden, 1, Northampton, 1, Revere, 1, Taunton, 2, Wellesley, 1, total, 33.

Encephalitis, infectious, was reported from Lowell, 1, total, 1.

Infectious hepatitis was reported from Haverhill, 1, Williamstown, 1, Wrentham, 19, total, 21.

Meningitis, meningococcal, was reported from Fairhaven, 1, Greenfield, 1, Natick, 1, Westport, 1, total, 4.

Meningitis, Pfeiffer-bacillus, was reported from Haverhill, 1, Sharon, 1, West Boylston, 1, total, 3.

Meningitis, pneumococcal, was reported from Fitchburg, 1, Warren, 1, total, 2.

Meningitis, undetermined, was reported from Taunton, 1, Tyngsboro, 1, Worcester, 1, total, 3.

Salmonellosis was reported from Erving, 2, total, 2.

Septic sore throat was reported from Acton, 1, Arlington, 1, Boston, 6, Groton, 1, Medford, 1, Natick, 1, Orleans, 2, Randolph, 1, Westport, 1, total, 15.

Tetanus was reported from Brookline, 1, total, 1.

Trachoma was reported from Foxboro, 3, total, 3.

Trichinosis was reported from Williamstown, 1, total, 1.

Typhoid fever was reported from Tewksbury, 4, total, 4.

Undulant fever was reported from Lenox, 1, Saugus, 1, total, 2.

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THE OCCURRENCE OF INFECTION AFTER PULMONARY RESECTION

A Study of the Effectiveness of Sulfonamides and Antibiotic Agents During a Six-Year Period (1942-1947)

CARROLL C MILLER, M.D.,* AND RICHARD H SWEET, M.D.†

BOSTON

AN ANALYSIS has been made of 427 cases of pneumonectomy and lobectomy during the years 1942 through 1947 at the Massachusetts General Hospital, and the results of the use of chemotherapeutic and antibiotic agents have been tabulated, with particular regard to complications caused by infection and to mortality. With few exceptions these complications occurred and were recognized during the postoperative hospitalization period, in several cases late recrudescence or fulmination of symptoms required readmission and further treatment. The latter cases have been included in the present study because the complications were considered to be the direct result of operation and its associated therapeutic program.

The years 1942 through 1947 were chosen because it was during this period that sulfonamides were first used, then penicillin and more recently streptomycin with increasing frequency. Sulfonamides were at first given in only a relatively small proportion of cases, and the manner in which they were administered in many cases would not be considered adequate in the light of the present concept of effective chemotherapeutic bacteriostasis. In 1944, when penicillin became available, the trend toward more complete prophylaxis and therapy was well under way, and by the end of 1946 all patients received penicillin. During the year 1946, a few selected patients received streptomycin in addition to penicillin, and in 1947 about half the patients received both drugs. It is the purpose of this study to show the definite decline in the rates of mortality and empyema during this six-year period as correlated with the use of chemotherapeutic and antibiotic agents.

In addition to the use of sulfonamides, penicillin and streptomycin during these six years, another

factor contributes strongly to the improvement in postoperative results. This is the diminishing use of the tourniquet in lung resections, and the adoption of the individual ligation technic in dealing with hilar structures. Such a technic was adopted before 1940,¹ and in the beginning of the series of cases reported here, the number of resections performed by the tourniquet method was already small. Later, in the past three years, the tourniquet and mass ligatures were never used as a method of controlling the hilus *en masse* proximal to the point of resection. In a very few cases it was necessary to employ the tourniquet temporarily to permit the removal of the lobe or lung, after this step the individual bronchovascular structures were isolated and separately secured. Judging from the high incidence of complications following the use of the tourniquet, and in recent years the infrequent occurrence of empyema with bronchopleural fistula or of massive fatal hemorrhage with the individual ligation technic, a distinct and significant, favorable influence may be attributed to the latter method. In recent years, another detail of technic used routinely at the hilus has been the careful suture of the bronchus with a single row of interrupted fine-silk sutures and complete capping of the closed stump with a pleural flap.²

Because of the diversity of diseases of the lung treated by resection and the number of different procedures performed, a mass grouping of all cases is of little significance except to give an over-all picture of results in a thoracic surgical service. On the other hand, a division of these cases into small sub-groups produces many series with no great importance from a long-range point of view. The value of individual group study, however, lies in the comparison afforded between the results of treatment in various diseases, and between different resection procedures (pneumonectomy, total lobectomy and segmental lobectomy in the various

*Assistant in surgery Harvard Medical School assistant in surgery Massachusetts General Hospital surgeon Palmer Memorial Hospital attending physician in thoracic surgery Cushing Veterans Administration Hospital Frammingham, Massachusetts.

†Associate clinical professor of surgery Harvard Medical School visiting surgeon Massachusetts General Hospital.

MASSACHUSETTS PHYSICIANS CLUB

A meeting of the Massachusetts Physicians Club will be held at the Hotel Kenmore, Boston, on Tuesday, April 12, at 8 30 p m Dr John F Conlin, director of medical information and education, Massachusetts Medical Society, will speak on the topic "Socialized Medicine"

All interested physicians and medical students are invited to attend

MASSACHUSETTS CHAPTER, AMERICAN ACADEMY OF GENERAL PRACTICE

The first annual clinical meeting of the Massachusetts Chapter of the American Academy of General Practice will be held in Boston on Friday, April 15 The morning session will be held at the Peter Bent Brigham Hospital, and the afternoon and evening sessions at the Hotel Statler

PROGRAM

- 9 00-10 00 a m Ward Rounds Francis D Moore, M D, surgeon-in-chief, Peter Bent Brigham Hospital, and Moseley Professor of Surgery, Harvard Medical School
- 10 00 a m-12 00 m Clinic — Amphitheater — George W Thorn, M D, chief, Medical Division, Peter Bent Brigham Hospital, Hersey Professor of Medicine, Harvard Medical School, associate professor of medicine, Johns Hopkins University School of Medicine (Cases will be presented and discussed by all services)
- 12 00-12 30 p m Registration (Parlor A)
- 12 30-1 30 p m Luncheon (Hancock Room — tickets, \$3 00)
- 1 30-2 15 p m Emotional Factors in Psychosomatic Illness Bearing on Early Childhood Relationships Alfred Ludwig, M D, assistant psychiatrist, Massachusetts General Hospital
Five minutes' intermission
- 2 30-3 05 p m Premarital Counseling James C Janney, M D, assistant professor of gynecology, Boston University School of Medicine
Five minutes' intermission
- 3 10-3 55 p m Rh Factor William C Moloney, M D, assistant professor of medicine, Tufts College Medical School
Five minutes' intermission
- 4 00-4 45 p m Treatment of Hypertension William Dock, M D, professor of medicine, Long Island College of Medicine, and director of medicine, College Division, Kings County Hospital, New York
Five minutes' intermission
- 4 50-5 35 p m Virus Diseases from the Clinical Point of View Conrad Wesselhoef, M D, clinical professor of infectious diseases, Harvard Medical School
- 6 00-7 00 p m Business meeting
- 7 30-8 30 p m Banquet (tickets, \$4 50)
- 8 30 p m Our Social Structure as a Cause of Psychosomatic Disorders Paul Graves Myerson, M D, assistant professor of psychiatry, Tufts College Medical School, instructor in psychiatry, Harvard Medical School, and physician-in-charge of nervous and mental diseases, Boston Dispensary

All addresses are designed for everyday practical application to the needs of the general practitioner

Doctors' wives are cordially invited to the afternoon and evening sessions and to the banquet

Dress will be informal

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

A meeting of the New England Society of Physical Medicine will be held in the Bigelow Amphitheater, Massachusetts General Hospital, on Wednesday, April 20, at 8 p m

The program, under the direction of Dr Arthur L Watkins, will be a Symposium on Rheumatoid Arthritis

ROSWELL PARK LECTURE AND MEDAL

Dr Evarts A Graham will deliver the Roswell Park Lecture of the Buffalo Surgical Society at the Kleinhans Music Hall, Buffalo, New York, on Thursday, May 5, at 9 p m The Roswell Park Medal for outstanding surgical achievement will be awarded to Dr Graham on this occasion

MASSACHUSETTS PHYSICIANS ART ASSOCIATION

The Massachusetts Physicians Art Association will hold its annual exhibit in conjunction with the annual meeting of the Massachusetts Medical Society at Worcester, May 24-26 Any member wishing to exhibit must send a list with the title, the medium, the evaluation and the approximate size of his pieces to Dr Charles E Ayers, 36 Pleasant Street, Worcester, Massachusetts, by April 25 Paintings must be framed for hanging Transportation and insurance will be arranged for without charge by the Massachusetts Physicians Art Association

ACADEMY OF NEUROLOGY

Establishment of the new American Academy of Neurology, latest of the specialty group organizations to come into existence, has been announced by its president, Dr A B Baker of Minneapolis

The purpose of the Academy is "to further and encourage the practice of clinical neurology and to stimulate teaching and research in neurology and allied sciences" The Academy has three grades of membership active membership open to all physicians who have been certified in neurology or neurology and psychiatry, junior membership open to those at present engaged in postgraduate study in neurology or awaiting certification, and associate membership for noncertified physicians whose interests are in allied fields

The first scientific meeting of the Academy will be held at French Lick Springs, June 1, 2 and 3, 1949

SOCIETY MEETINGS AND CONFERENCES

- JANUARY 7-APRIL 13 American College of Surgeons. Sectional Meetings Page xi issue of December 23
- APRIL 1-28 Consultation Clinics for Crippled Children in Massachusetts Page 489 issue of March 24
- APRIL 11, 12 AND 14 Boston City Hospital House Officers Association. Page 587
- APRIL 12 New England Society of Anesthesiologists Page 490 issue of March 24
- APRIL 12 Harvard Medical Society Page 587
- APRIL 12 Massachusetts Physicians Club Notice above
- APRIL 14 Practical Aspects of the Treatment of Hypertension Dr John C Leonard. Pentucket Association of Physicians 8 30 p m Haverhill
- APRIL 14-17 American College of Allergists Page 276 issue of February 17
- APRIL 15 Massachusetts Chapter American Academy of General Practice Notice above
- APRIL 20 New England Dermatological Society Page 528 issue of March 31
- APRIL 20 New England Society of Physical Medicine Notice above
- APRIL 30 Long Island College Alumni Association Page 528 issue of March 31
- MAY 4 New England Obstetrical and Gynecological Society Springfield Country Club Springfield
- MAY 5 Suffolk Censors Meeting Page 276 issue of February 17
- MAY 5 Roswell Park Lecture and Medal Notice above
- MAY 7 New England Society of Anesthesiologists Page 401 issue of March 10
- MAY 10 Harvard Medical Society. Lower Out Patient Department Amphitheater Massachusetts General Hospital
- MAY 16-19 American Urological Association Biltmore Hotel Los Angeles California.
- MAY 18-21 Association for Physical and Mental Rehabilitation. Page 401 issue of March 10
- MAY 24-26 Massachusetts Medical Society Annual Meeting Worcester Memorial Auditorium Worcester
- MAY 24-26 Massachusetts Physicians Art Association Notice above
- MAY 26-28 American Gout Association Hotel Loraine Madison Wisconsin
- MAY 30-JUNE 3 International Congress on Rheumatic Diseases. Page 800 issue of November 18
- JUNE 1-3 Academy of Neurology Notice above
(Notices concluded on page xiv)

empyema, but thereafter there was a decline to 0. It should be stated at this point that during the period 1942-1947 the procedures were carried out

been our experience that patients who undergo a segmental resection do not have so smooth a convalescence as those who undergo total lobectomy^{5 6}

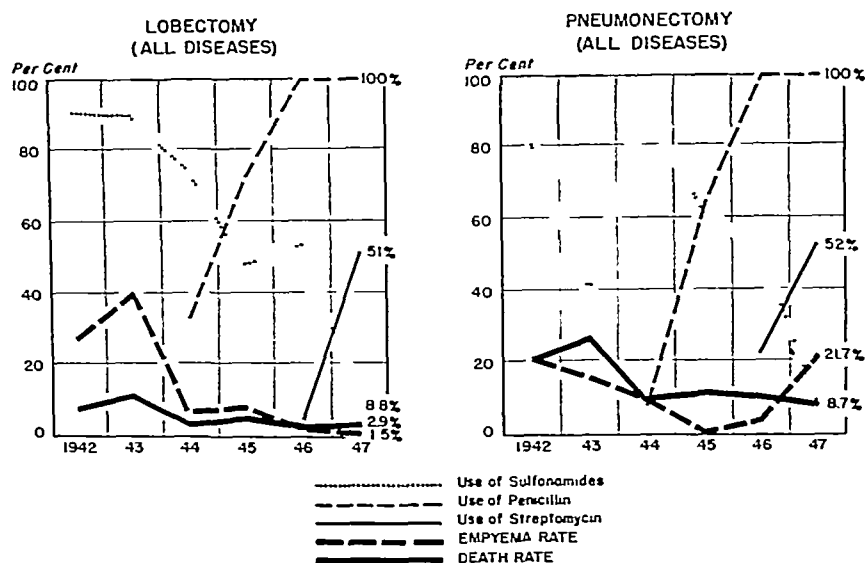


FIGURE 2 Incidence of Empyema and Death in Relation to the Use of Sulfonamides, Penicillin and Streptomycin

by several operators of varied experience, and this fact may also have influenced the statistical results.

Lobectomy for bronchiectasis presents the best immediate postoperative prognosis of all the diseases

This discrepancy seems to be due less to immediately resultant infection than to technical intrapulmonary or intrapleural factors such as infarction of a lobar segment by inadvertent interruption of a major

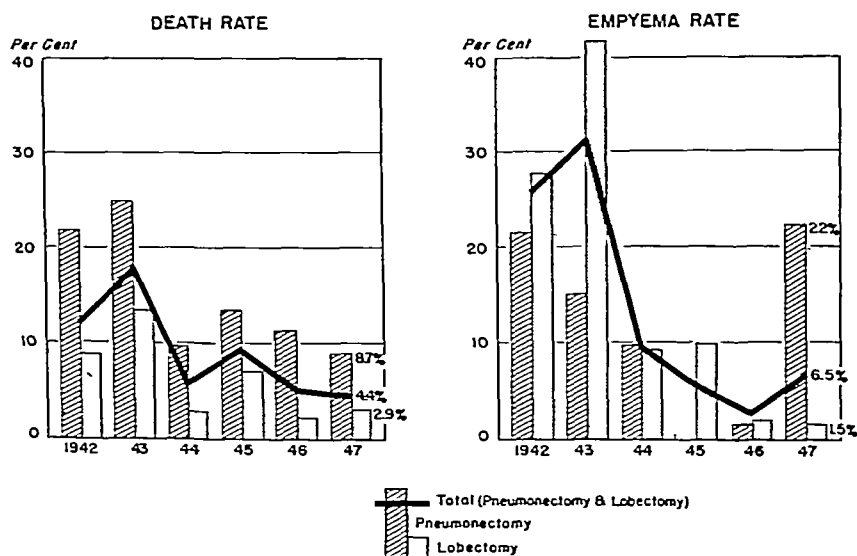


FIGURE 3 Mortality and Empyema Rates for Pneumonectomy and Lobectomy

in experienced hands (Fig 1). With the continued trial of segmental resection methods, there may be a variation in the complication-rate curve. It has

blood vessel to that segment, plugging of a bronchus with resulting atelectasis, inadequate aspiration of the bronchial tree during or after operation, com-

lobes) A suggested prognosis in each type of case is thereby offered

Four major disease groups are considered These are bronchiectasis, lung abscess, tuberculosis and carcinoma As indicated in Figure 1, lobectomy for bronchiectasis in the years 1943, 1944 and 1946 was associated with no mortality in 60 cases and with a total mortality for the six years of 3.9 per cent, in this group there were 4 cases of empyema in 1943, 1 in 1944, 3 in 1945, and none in 1946 or 1947 Lung abscess was associated with a relatively high incidence of complications, but improvement is seen in the last two years This incidence contributes mainly to the striking increase of empyema in all cases in 1943 In the most recent report on the treatment of lung abscess at the Massachusetts General Hospital, the importance of

and streptomycin In six years the gross mortality rate for all diseases treated by pneumonectomy and lobectomy dropped from 21.4 per cent and 8.3 per cent to 8.7 per cent and 2.9 per cent respectively, in 1947 none of the deaths were due to sepsis but instead to technical difficulties during operation (uncontrollable hemorrhage and plugging of contralateral bronchial tree with mucus or blood) and in 1 case to later cardiorespiratory failure manifested at autopsy by pulmonary congestion and edema In the first five years, through 1946, the empyema rate similarly dropped from 21.4 per cent and 27.7 per cent to 3.7 per cent and 2 per cent respectively In 1947 there were 5 empyemas in the group of 23 pneumonectomies (21.7 per cent) and 1 empyema among 68 lobectomies (1.5 per cent) Three of these, which were total empyemas subsequent to

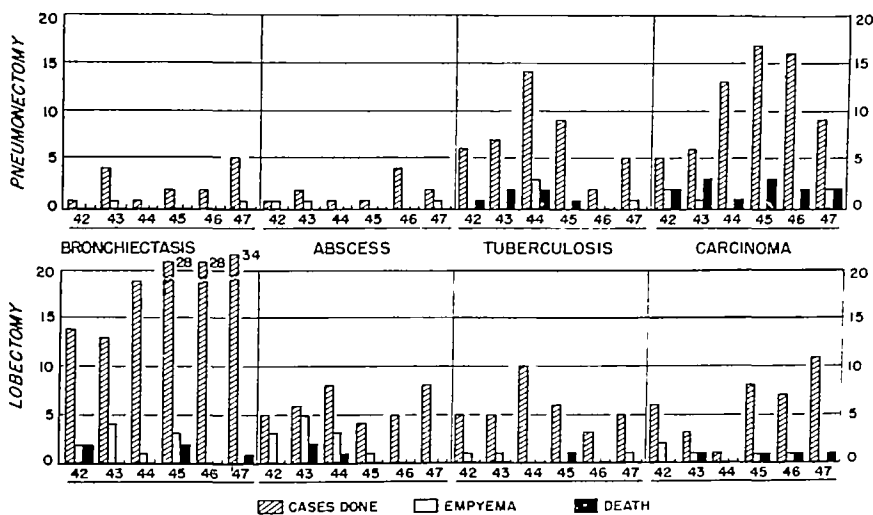


FIGURE 1 Incidence of Empyema and Death Following Pneumonectomy and Lobectomy, Arranged in Groups of Bronchiectasis, Abscess, Tuberculosis and Carcinoma and Further Subdivided into Yearly Blocks

lobectomy in selected cases was discussed as a more desirable method of treatment than drainage.³ As a result of the adoption of this policy, more lobectomies and pneumonectomies have been performed for this disease in the past few years. The tuberculosis data are essentially those reported in 1946, with the inclusion of the rest of the cases in that year and those in 1947, subsequent to that report.⁴ The cases of carcinoma bring into consideration other factors (resection for palliation, general condition of the patients and complicating infection) that may influence death and empyema rates, but they are not within the specific scope of this paper.

Figure 2 shows the improvement in empyema rates and death rates for lobectomies and pneumonectomies as separate groups coincident with the use at first of sulfonamides and later of penicillin

pneumonectomy, became evident several months after discharge following an apparently smooth convalescence. During these operations there had been no unusual, obvious contamination. Of the 5 empyemas complicating pneumonectomy, 2 were after operations for carcinoma, and 1 each after operations for abscess, bronchiectasis and tuberculosis.

Figure 3 demonstrates the same trends shown in Figure 2, but in simplified detail and in a different combination of data. During the six-year period the improvement in death rate after pneumonectomy, lobectomy and in the total number of resection cases grouped together is readily seen. A similar decrease in the empyema rate is obvious.

Figure 4 shows the total number of deaths during the six years as compared with the number of deaths associated with empyema. In 1944 it is seen that half the patients (2 out of 4) who died had

empyema, but thereafter there was a decline to 0. It should be stated at this point that during the period 1942-1947 the procedures were carried out

been our experience that patients who undergo a segmental resection do not have so smooth a convalescence as those who undergo total lobectomy^{5 6}

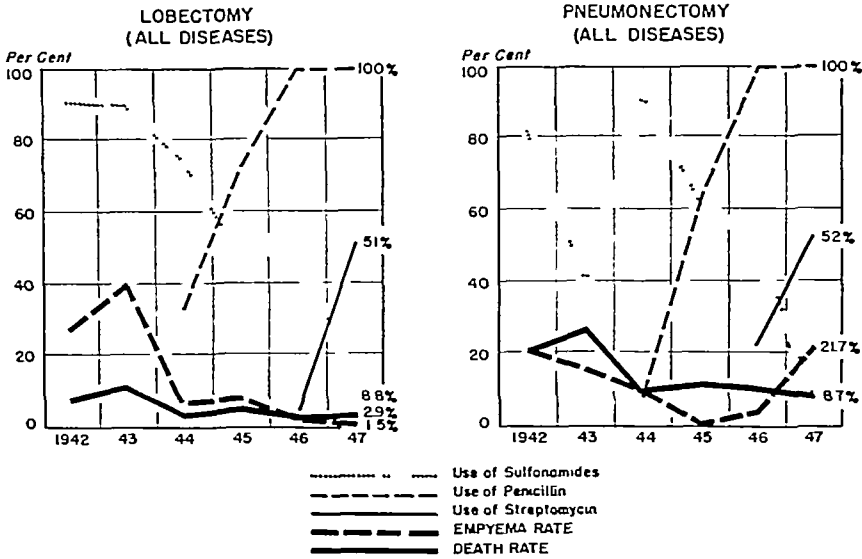


FIGURE 2 Incidence of Empyema and Death in Relation to the Use of Sulfonamides, Penicillin and Streptomycin

by several operators of varied experience, and this fact may also have influenced the statistical results.

Lobectomy for bronchiectasis presents the best immediate postoperative prognosis of all the diseases

This discrepancy seems to be due less to immediately resultant infection than to technical intrapulmonary or intrapleural factors such as infarction of a lobar segment by inadvertent interruption of a major

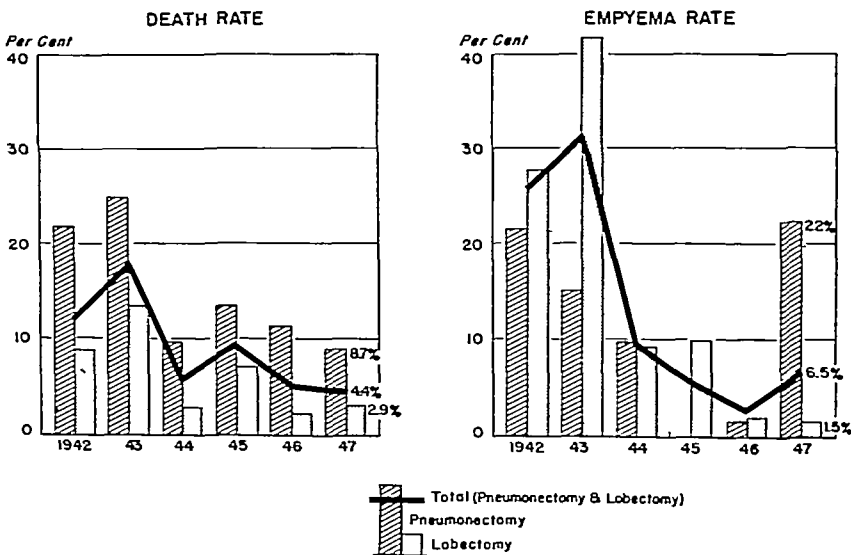


FIGURE 3 Mortality and Empyema Rates for Pneumonectomy and Lobectomy

in experienced hands (Fig 1). With the continued trial of segmental resection methods, there may be a variation in the complication-rate curve. It has

blood vessel to that segment, plugging of a bronchus with resulting atelectasis, inadequate aspiration of the bronchial tree during or after operation, com-

pression atelectasis by accumulated pleural effusion, too extensive suturing of lobe surfaces in order to obtain pleuralization or hemorrhage into lung parenchyma beneath the suture line. Recently, according to the suggestion of other writers,^{5, 7, 8} several of the surgeons in this hospital have been either leaving the cut surface of the remaining segment of lung uncovered by pleura or using a circumferential marginal flap of pleura left purposely on the remaining segment during resection to be sutured over the raw parenchymal surface. The patients in whom this detail of technic has been used have appeared to recover more uneventfully than

chemotherapeutic and antibiotic agents is a valuable safeguard because although healing of the lesion may not occur without the benefit of surgery, the surrounding pneumonitis can be appreciably reduced as shown by roentgenograms, and spreading invasive infection, empyema and wound sepsis may be prevented in a large majority of cases.

In patients with wet bronchiectasis, the use of aerosol penicillin has reduced the amount of sputum and increased the patient's sense of well-being.⁹ This effect is somewhat more marked when penicillin is nebulized and inhaled than when it is given by intramuscular injection alone (Aerosol streptomycin was administered with aerosol penicillin to 15 patients in the whole series).

Mention should also be made of the use of penicillin and streptomycin injected into the pleural cavity after the demonstration of frank empyema. Two cases in this series were cured in this way without rib resection for drainage, one with penicillin and one with streptomycin, and 4 others were unsuccessfully treated. Such therapy must be early, massive (at least 100,000 units of penicillin or 1 gm of streptomycin, or both, daily) and persistent until the infection is controlled. As repeatedly emphasized in the recent and current literature, when a persistently recurring accumulation of pleural fluid following lobectomy or pneumonectomy is shown by culture, or by direct smear at the time of thoracentesis, to be contaminated by bacteria, penicillin or streptomycin, or both, depending on the nature of the infecting organisms, should be injected immediately and the therapy continued daily. The injection should be preceded by the aspiration of as much of the exudate as possible. It is important to institute this regimen early since, especially in cases of lobectomy, after three or four days the effusion may become loculated by the fibrinous process within it, and it is no longer possible to treat the empyema as a single cavity. During the diminution in amount of fluid as demonstrated by roentgenograms and the results of aspiration, and when the febrile reaction subsides, this medication can be administered less frequently and presently stopped.

The presence of a bronchopleural fistula that complicates an empyema suggests the interesting query, Is the fistula the cause or the result of the empyema, and how effective can specific bacteriostatic medication be in the presence of an open bronchial stump? An immediate, obvious answer is that if the bronchial suture line opens and remains open, contamination will occur and persist in spite of the use of antibiotic agents. This, it is believed, is not necessarily the case. If bacterial activity in the vicinity of a bronchial stump is adequately inhibited by the drug employed by virtue of both its systemic and its intrapleural concentrations, and if tissue healing proceeds at a normal

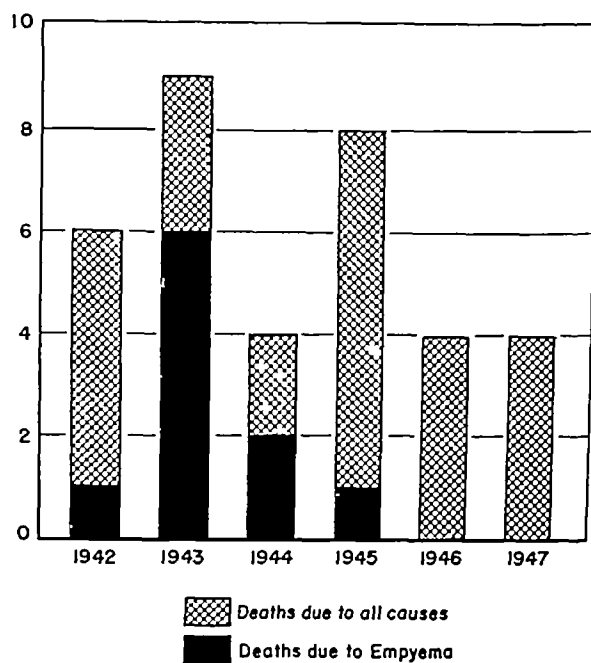


FIGURE 4 Total Number of Deaths for Each Year Compared with the Number of Deaths Complicated by Infection

many of those in whom the clamp-suture or non-stripping technic has been employed.

It should be emphasized that in the majority of cases of bronchiectasis, lung abscess or tuberculosis there is a mixed infection, involving organisms that may be resistant to currently available drugs. The development of more effective agents may be necessary to obtain better results. For example, streptomycin has been used together with penicillin, both in supposedly adequate large doses in a number of such cases. It was interesting to observe that often in these cases there was no demonstrable response to drug therapy as indicated by the temperature chart preoperatively. After operation, however, the course was extremely smooth, with no complications. This suggests that the most important factor of treatment is the extirpation of diseased tissue. On the other hand, protection with

rate, the bronchial fistula may well heal before the process becomes a chronic one. Thus, it is clearly indicated that satisfactory antibiotic protection must be combined with a careful technic and a thoroughly supportive nutrient regimen.

In this whole series, there were reported 11 bronchopleural fistulas, 1 in 1942, 7 in 1943, 2 in 1944, 1 in 1946, and 2 in 1947. The one patient in 1946 received penicillin before and after operation, and healed his fistula spontaneously within two weeks. The others in previous years received only sulfonamides, and in those who survived, healing was slow and prolonged. One of the 2 patients in 1947 who developed a fistula had had a pneumonectomy for tuberculosis and was given penicillin before and after operation, and streptomycin postoperatively only. The other, a patient who had a pneumonectomy for bronchiectasis, received penicillin intramuscularly and by the aerosol route preoperatively, in the chest at operation, and intramuscularly postoperatively — and streptomycin, only at operation, in the pleural cavity. The former was discharged to a sanatorium with the fistula still patent, and the latter required first a rib resection for drainage and later a thoracoplasty. Patients who developed fistulas in other years also had protracted convalescences.

The trend in fistula development closely follows that of empyema, and the problem of prevention should entail, in addition to the technic of closing the bronchus, the prophylactic and therapeutic principles used in the prevention or cure of infection in general.

A survey of pneumonectomy and lobectomy cases combined, with respect to sulfonamide, penicillin and streptomycin administration, reveals that in 1942, 6 patients received no drug therapy, and of these, 1 had empyema, in this group in which the drug was used there seems to be little or no correlation between the method of administration and the incidence of empyema. Twenty patients received a sulfonamide in the pleural cavity at operation and by parenteral administration postoperatively, and 5 had empyema. Twelve received it postoperatively* only, and 3 had empyema. Two received it preoperatively and postoperatively with no empyema. Seven received it in the pleural cavity at operation only, and there were 4 empyemas. One received it preoperatively and in the chest without resulting empyema. One received it preoperatively only and had empyema. One received it by all three methods and had empyema. Of the 3 fatal cases with infection in the form of empyema or parenchymal sepsis, none had what would now be called an adequate dosage of sulfonamide. Of course, these data are influenced strongly by the type of case (Fig 1), but a general conclusion from

the group as a whole indicates unsatisfactory protection with sulfonamides.

In 1943, a single case of empyema occurred among 15 patients who received no sulfonamide. Sixteen received the drug postoperatively, with 5 empyemas. Ten received it before and after operation, with 4 empyemas. In 4 it was used in the chest and postoperatively, with 3 empyemas. In 4 it was used preoperatively and postoperatively and in the chest, with 3 empyemas. Two received it preoperatively, with no empyema. Three of the 6 patients who died from sepsis had sulfonamide before and after operation, and of these, 1 received sulfanilamide in the pleural cavity at operation. The remaining 3 had it only postoperatively. The comment made in the above paragraph applies also to the year 1943, but the ineffectiveness of sulfonamides becomes more apparent.

In 1944 there were 2 cases of empyema among 56 patients who received sulfonamides alone, but on detailed analysis, the drug was given much more adequately than in previous years. Eleven had penicillin alone, with 2 empyemas, and 6 had both penicillin and sulfonamide, with 3 empyemas (the penicillin dosage and time of administration were inadequate). Sulfonamide was used in the chest at operation only once during this year and never thereafter. The 4 patients who died received a sulfonamide before and after operation, and 2 of these were given penicillin late in the postoperative period, but to no avail. Two of the 4 had definite empyema, in the remaining 2, pneumonia was suspected but not proved.

In 1945 sulfonamide alone was given to 23 patients, with 1 empyema, the drug, again, having been administered more thoroughly in most cases. Thirty-nine patients had penicillin alone, with 4 empyemas. Twenty-three had both, with no empyema. The 1 patient who apparently died of sepsis received sulfonamide preoperatively and postoperatively but no penicillin.

In 1946 penicillin alone was administered to 35 patients, and 1 developed empyema, which was cured by postoperative intrathoracic injection of penicillin. Forty-one received both penicillin and sulfadiazine, and there was 1 empyema. In this year 4 patients received streptomycin by aerosol administration preoperatively, and intramuscularly postoperatively, and an additional patient had it instilled in the chest at operation only. None of these had sepsis complicating recovery, and there were no deaths from sepsis.

During 1947, a year in which 6 cases were complicated by empyema, all patients (91) were given penicillin at some time during their hospital course, either before or after operation, or both. Some received aerosol penicillin before, and some after, operation. A large majority (69 patients) received an intrapleural injection at the conclusion of operation. Streptomycin was used with penicillin in

*Unless specifically mentioned as being administered intrapleurally or in the chest, these drugs were given orally or intravenously (sulfonamides) or intramuscularly (penicillin and streptomycin).

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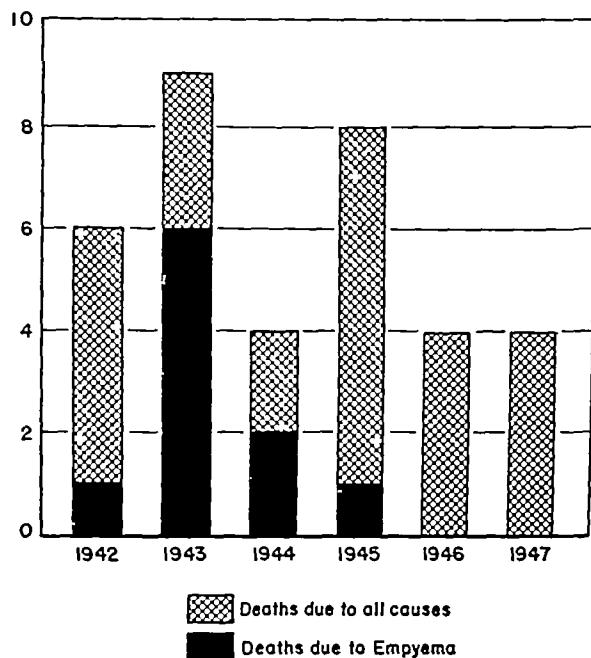


FIGURE 4. Total Number of Deaths for Each Year Compared with the Number of Deaths Complicated by Infection

many of those in whom the clamp-suture or non-stripping technic has been employed.

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amide alone — a fact that suggests that for optimum protection penicillin should be combined with a complementary agent

Figure 6 demonstrates the gradual shortening of the hospitalization period in each year with the gratifying conclusion that in addition to the all-important improvement in postoperative results, a monetary saving for the patient and an increased availability of beds for the hospital are achieved

The present routine chemotherapeutic program used for lung resection consists of the intramuscular injection of 300,000 units of penicillin (100,000 units every eight hours) and 1 gm of streptomycin (0.25 gm four times a day) daily for two days before operation. When there is fever or other signs and symptoms of toxicity, profuse sputum or evidence of pneumonitis by roentgenologic examination, penicillin may be administered for a week or ten days preoperatively. Aerosol penicillin, 50,000 units in 1 cc of physiologic saline solution, with or without streptomycin (0.25 gm) as indicated, is administered four times a day when expectoration is profuse preoperatively. In a few cases this form of chemotherapy has been used effectively in reducing the volume of sputum postoperatively. At operation, before the chest is closed, 100,000 units of penicillin and 1 gm of streptomycin dissolved in 30 cc of physiologic saline solution are instilled into the pleural cavity. Intramuscular injection of both drugs (100,000 units of penicillin and 0.25 gm of streptomycin every six hours) is continued for five or six days, or until the patient's temperature chart has been normal for three days. The use of penicillin and streptomycin intrathoracically in the event of suspected empyema after operation has been described above. When infection is present either before or after operation, the dosage and frequency of administration are increased.

Since the conclusion of the period covered in this study, streptomycin has been administered in addition to penicillin in *all* cases of lung resection as a routine adjunct in therapy with the hope that the figures herewith presented will be improved in immediately succeeding years.

SUMMARY AND CONCLUSIONS

Four hundred and twenty-seven cases of lung resection at the Massachusetts General Hospital in a six-year period (1942-1947) are reviewed with the specific intent of demonstrating the trend of infection and mortality rates in reference to the use of chemotherapeutic and antibiotic medication. The incidence of empyema and septic deaths is especially stressed. Intrapulmonary infection postoperatively is not considered in detail because of the difficulty in determining the exact extent and nature of the lesion in cases that do not come to subsequent operation or autopsy. Wound sepsis has been practically nonexistent in this series of

operations. Silk-suture material has been used almost invariably in the chest-wall closure.

The broad groups of lobectomy and pneumonectomy, as well as the four major disease entities in pulmonary pathology, — bronchiectasis, abscess, tuberculosis and carcinoma, — have been analyzed with respect to the obvious improvement in operative results. The data show a significant decline in infection and mortality rates, in the ratio of nonseptic to septic deaths and in the duration

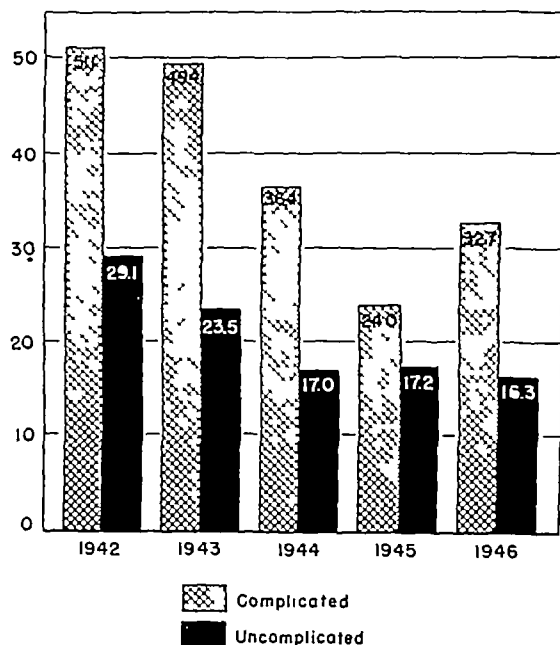


FIGURE 6 *Average Number of Days Spent in the Hospital after Lung Resection in Both Complicated and Uncomplicated Cases*

of hospital confinement for patients with uncomplicated and complicated postoperative courses.

Finally, a brief outline is given of the current regimen of protective medication used.

Chemotherapeutic and antibiotic agents seem to have a valuable place in the program of surgical treatment of pulmonary disease.

Drug therapy must be adequate and complete — that is, it must be given preoperatively and postoperatively. The use of penicillin and streptomycin in the pleural cavity at the conclusion of a resection cannot be easily evaluated, but it is assumed that it contributes to better results.

All cases must be carefully studied from a bacteriologic standpoint, and the proper agent and dose selected for the individual patient.

Early postoperative bronchoscopic aspiration should be used when there is failure of expansion as a result of bronchial obstruction, and prompt thoracentesis should be done in the presence of appreciable effusion. Intrathoracic instillation of

the same manner of administration in 46 cases Sulfonamides were given (without streptomycin) in 5 cases in the early part of the year before streptomycin became freely available, and in 3 additional cases with streptomycin as well. One of the latter patients received a sulfonamide postoperatively specifically for a bladder infection, and the other 2 had it preoperatively with streptomycin used only in the pleural cavity at operation.

A detailed analysis of the drug therapy given in the cases of empyema in 1947 indicates an inadequacy of streptomycin administration in the light of our present concept, for only 1 patient received streptomycin preoperatively and only 2 received it intrapleurally. (Four of the tuberculous patients

some of these organisms to the medication given. In the cases of tuberculosis we have been particularly mindful of this problem when streptomycin has been given for a period of several weeks before proposed operation and when its use after operation has been planned. Sensitivity studies have usually been done in the sanatorium before the patient comes to us, and care has been taken to avoid prolonged administration with its danger of both desensitization of the organism and toxicity to the patient. In the nontuberculous patients, also, it is indeed probable that certain cases that responded poorly to antibiotics did so because of natural or acquired resistance of the infecting organisms. However, the over-all improvement seen

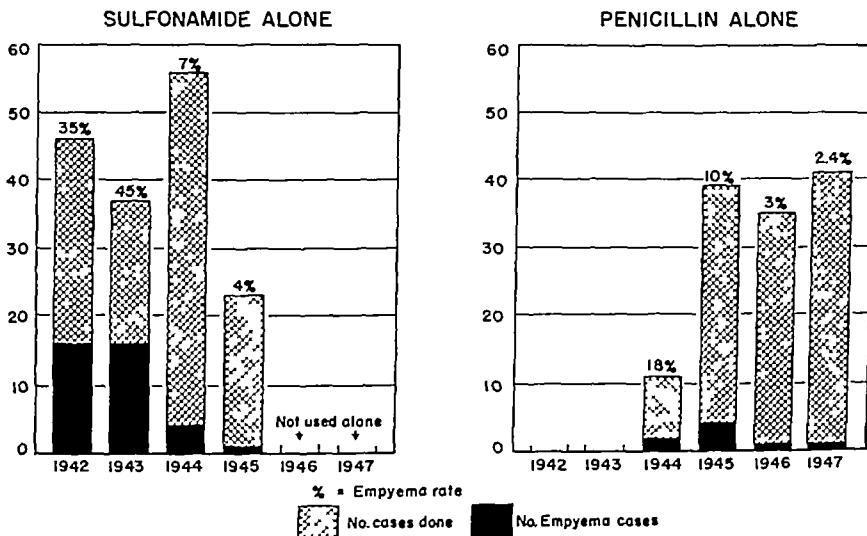


FIGURE 5 Incidence of Empyema in Each Year, First with Sulfonamide Administration Alone, and Then with Penicillin Alone

were not given intrapleural streptomycin, but of these only 1 developed empyema.) Three of the 6 patients with empyema received penicillin adequately (according to present standards), but 2 received it only postoperatively. Five of these cases were pneumonectomies—for carcinoma (2), abscess (1), bronchiectasis (1) and tuberculosis (1). The 1 lobectomy was done for pneumatocele. In none of the cases was there any error in technic or untoward factors that had not been encountered many times previously. Thus, there seems to be at hand no satisfactory explanation for the disappointing rise (Fig. 3) in the empyema rate for pneumonectomy in this year as contrasted with that of the preceding three years.

Except in rare cases in the total group of cases reported here, studies of the sensitivity of infecting organisms to antibiotic substances were not done, and the agents used were administered empirically without specific regard for possible resistance of

in this six-year period suggests that in general the sensitivity problem per se does not definitively affect the trend of results. In most cases the infecting organisms appear to be susceptible, or the antibiotic agent is not administered for a sufficiently long time to alter the sensitivity of the organism. On the other hand, more detailed attention to these factors should enhance the improvement already effected, and give a more accurate picture of the role that these agents play in certain refractory cases of postoperative infection.

The relative decline of empyema rate associated with the use of each of the two earliest chemotherapeutic agents alone (sulfonamide and penicillin) is indicated in Figure 5, in an attempt to evaluate the trend in the respective series. There is a more consistent drop to a lower level with penicillin than with sulfonamides. However, it will be noted that in 1944 and 1945, there was a higher incidence of empyema with penicillin alone than with sulfon-

bulk of the fibrinogen of normal human plasma and a globulin active in reducing the clotting time in hemophilia¹⁰). The fibrinogen content of the total plasma was roughly estimated for the patient, and 4.80 gm of Fraction I (24 vials) dissolved in distilled water was given rapidly intravenously by syringe. The clotting time at 2:30 p.m. was 5 minutes, and the bleeding time was 5 minutes. The patient's general condition had deteriorated; she was stuporous and vomited brownish fluid. Another 1000 cc. of blood was started, and a sterile vaginal examination was attempted but the patient began to flow profusely from below. She was quickly prepared, and at 4:00 p.m. a rapid cesarean section was performed. The uterus was plum colored and infiltrated with blood, and it was removed by a rapid hysterectomy. The surgeons and observers agreed that after the removal of the uterus bleeding seemed to cease, subsequently no further bleeding from the gums or into the skin was noted.

After the operation the patient developed a moderate degree of shock, the blood pressure was 60/40, and the pulse 160. After a transfusion of 1000 cc. of whole blood she rallied, at 7:00 p.m. the clotting time was less than 1 minute and the bleeding time was normal. At 8:00 a.m. on February 2, the patient voided and her general condition was fairly good. The clotting time was 1 minute, no abnormal bleeding was noted but because of a low hematocrit (22 per cent) a transfusion of 1000 cc. of blood was given.

The subsequent course was uneventful, the bleeding and clotting times were within normal limits, and although the patient was literally "black and blue" from head to foot, she dangled her legs on February 3, was out of bed on February 5 and was discharged on February 12. She was rechecked periodically for several months after this episode, and all blood studies were within normal limits.

Autopsy on the infant revealed a macerated fetus with no special findings. The uterus and placenta were studied by Dr. Arthur Hertig, who reported the following pathological findings:

Examination shows a slightly premature placenta. Probable intrauterine death is evidenced by fibrosis of villi. There is premature separation of the toxic type and moth-eaten degeneration of trophoblasts. Hemorrhage into decidua is noted. The uterus is of the couvulaire type.

Owing to marked post-mortem changes, the amount of syncytial degeneration is impossible to evaluate. There is no atheromatosis of decidual sinusoids.

Unfortunately the uterus, after its removal, was placed in formalin solution for about 10 minutes. Subsequently studies on extracts of the organ (by Dr. O. W. Smith) failed to reveal any evidence of fibrinolytic activity, but it was believed that the formalin may have destroyed the labile fibrinolysin.

The most important blood specimens were those obtained at 6:00 a.m. and 8:00 a.m. on February 1, before the administration of blood and fibrinogen. Since only small amounts of these oxalated and clotted blood specimens were available, experiments were limited. The immediate problem was to determine the cause of incoagulability of the blood and this was investigated, insofar as possible, by a study of each of the various clotting factors.

There was no evidence in either clinical or laboratory studies of liver damage in this patient. Although rare, hypoprothrombinemia has been reported in the absence of obstructive jaundice and liver disease, in this case the prolonged prothrombin clotting time suggested the possible diagnosis of hypoprothrombinemia. However, the fibrin clot formed during the test was so scanty that the lack of fibrinogen was suspected. The addition of thrombin to the blood and plasma specimens obtained at 8:00 a.m. failed to produce coagulation and this finding, in the light of subsequent observations, proved that the lack of fibrinogen was the cause of the clotting defect.

Addition of calcium to blood and plasma of this patient did not restore coagulability; consequently lack of calcium was readily ruled out.

No evidence of an anticoagulant was found in the patient's blood. Direct addition of pretransfusion whole blood and plasma to normal blood and plasma caused no inhibition of clotting.

Addition of potent bovine thrombin to pretransfusion specimens of the patient's whole blood and plasma did not cause coagulation. Subsequently fibrinogen determinations

carried out on oxalated pretransfusion specimens revealed a complete absence of fibrinogen. Specimens obtained during the evening following operation showed a fibrinogen level of 0.5 gm per 100 cc., and specimens obtained three days postoperatively gave a fibrinogen value of 0.35 gm per 100 cc. It seems unquestionable that the incoagulability of the patient's blood was due to a complete lack of fibrinogen.

Afibrinogenemia is a rare disease that has been reported as a congenital defect and in severe liver disorders^{11, 12}. Neither of these causes could be established in this case. In view of the recent work of the Smiths^{4, 6, 12-15} and the studies of other investigators on fibrinolysin, the explanation for the lack of fibrinogen and of fibrin in this patient seemed to rest most logically on the presence of a fibrinogenolysin or a fibrinolysin.

Observations on the small clot formed in the blood specimen obtained at 6 a.m. after standing overnight showed that the clot, although small, had not lysed. For several days after delivery, experiments were carried out on the pretransfusion serum specimens to demonstrate the presence of a fibrinolysin, but no lysis of clots formed from fibrinogen (Fraction I) and normal plasma was observed. However, experiments on the pretransfusion plasma (kept in a deep freeze) indicated that when fibrinogen (Fraction I) was added to this plasma and allowed to stand at 37°C overnight, no clotting occurred on the addition of thrombin to the mixture. On the other hand, when normal human plasma was used as the source of fibrinogen a clot occurred when thrombin was added. This observation seemed to indicate that there was a protective antifibrinogenolysin in the normal plasma and suggested that the lack or destruction of antifibrinogenolysin was the cause of the afibrinogenemia in this patient.

DISCUSSION

It seems well established that the cause of the *coagulation defect* was the complete lack of fibrinogen. The occurrence of acquired afibrinogenemia is extremely rare, especially in the absence of liver disease. Dieckmann,² in 1936, reported that in 5 of 11 cases of abruptio placentae extremely low fibrinogen levels were found, after delivery fibrinogen returned to normal. In one case Dieckmann² states that "the blood failed to clot in the test tube" and this patient "bled from the gums, stomach, uterus and into subcutaneous tissues." No detailed studies on the clotting mechanism were carried out in Dieckmann's cases, and he attributed the clotting defect to a lowering of the fibrinogen content due to blood loss and the mobilization of fibrin at the site of placental separation.

In 1946 Tagnon and his associates¹⁶ described, in a paper on fibrinolysis, a patient with incoagulable blood after a post-partum hemorrhage. Fibrinogen added to the patient's plasma, which had been collected shortly before death, clotted, but the clot dissolved within an hour. This group of investigators postulate that shock, especially that associated with hemorrhage and burns, results in anoxia with a release of a tissue factor that may have a precipitating effect on the production of fibrinolysin. However, in the case reported above, the patient was not in shock when her blood was first found to be incoagulable, moreover, fibrinolytic activity in the blood has been described in a variety of conditions unassociated with shock.

It must be admitted that the present knowledge of fibrinogenolysis and fibrinolysis is in a confused and uncertain state. MacFarlane¹⁷ states that

massive doses of penicillin and streptomycin may be effective in preventing or curing empyema

Aerosol penicillin with or without streptomycin is of benefit when sputum is profuse

It is believed that these agents also minimize the tendency to the development of pneumonitis in atelectatic areas of lung tissue, which frequently occurs postoperatively

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ACQUIRED AFIBRINOGENEMIA IN PREGNANCY*

WILLIAM C. MOLONEY, M.D.,† WILLIAM J. EGAN, M.D.,‡ AND ARTHUR J. GORMAN, M.D.§

BOSTON

ONE of the most catastrophic events in obstetric practice is the occurrence of a fulminating hemorrhagic diathesis usually associated with toxemia of pregnancy and toxic separation of the placenta. Although uncommon, this usually fatal disorder has been encountered by most obstetricians of long experience.¹⁻³ For many years it has been suspected that there was a common etiologic background for this hemorrhagic disorder and toxemia of pregnancy, and it has been postulated that the uterus and its contents were the source of a toxic factor.²⁻⁶ In spite of the various theories advanced no toxic substance has actually been identified in the blood of patients with toxemia of pregnancy.

Although the occurrence of incoagulable blood, in what has been called the "calamitous" toxemic patient, has been described by a number of authors,²⁻³ the characteristics of the defective clotting mechanism have not been clearly established. Recently, a patient was encountered with this hemorrhagic disorder in pregnancy, and the following report is an account of the case with certain observations on the nature of the incoagulability of the blood.

CASE REPORT

Mrs. T. W., a 25-year-old gravida II, whose estimated date of confinement was January 30, 1948, entered the hospital because of lower abdominal pain and bleeding from the gums. She had been well throughout her pregnancy except for a prior admission to the hospital at about the 8th month for lower abdominal pain. At that time after 48 hours she was discharged with a diagnosis of false labor, the blood pressure and urinary findings were within normal limits. Throughout the last month of pregnancy she had lower abdominal discomfort and some dull pain, but at no time was there elevation of the blood pressure or abnormal urinary findings.

On the evening of January 31 the lower abdominal pain became more severe, and about 10:00 p.m. the patient noted spontaneous bleeding from the gums. Both the pain and

bleeding from the gums became worse, and she was admitted to the hospital at 1:00 a.m. on February 1.

The past and family histories were free of any evidence of abnormal bleeding tendency. In general her health had been excellent except that at the age of 15 the gall bladder and appendix had been removed. The patient had had one prior pregnancy, 2 years before, she had given birth uneventfully to a full-term, normal child. There was no history of toxemia during the first pregnancy, but she had noticed slight bleeding from the gums.

The patient complained of severe lower abdominal pain, and the uterus was tense and painful to palpation. The fetal heart was not heard. An unusual feature was the obvious bleeding from the gums, there was no ulceration, but the gingival margins were slightly swollen and free bleeding occurred from these areas. At 4:00 a.m., after an obstetric consultation, the clotting time was found to be greatly prolonged. Two hours later the patient was in good general condition, but the bleeding from the gums was more profuse and it was noted that wherever injections or venipuncture had been performed, ecchymotic areas appeared. Moreover, the uterus seemed larger and more painful. At this time, more detailed blood studies were carried out. The clotting time was rechecked at 37°C by a modified Lee and White⁷ technique, and the blood clotted as a poor gel only after 16 hours. The capillary fragility test was strongly positive, and the bleeding time (Duke⁸ method) was 14 minutes. Later, this puncture wound bled spontaneously for several hours. Blood smears showed numerous platelets present. The prothrombin clotting time (Quick⁹ procedure) was prolonged to 42 seconds, with a 14-second control, and it was noted that the fibrin clot was a poor film. Because of the prolonged prothrombin clotting time, 60 mg. of vitamin K was given intravenously at 8:00 a.m. At 8:30 a clotting time showed the blood to be incoagulable, after standing for 24 hours no clot formed. A transfusion of 1000 cc. of whole blood was given, and at 11:00 a.m., the determination of the clotting time was repeated. A poor gel formed in 15 minutes, but it was not a good blood clot and another 1000 cc. of blood was administered. The patient at this time was bleeding freely from the gums, and the bleeding-time puncture wounds were also bleeding spontaneously. Vaginal staining began, and the patient lapsed into a semicomatose state. Meanwhile further studies on the blood specimens taken at 6:00 and 8:00 a.m. revealed that the addition of thrombin did not cause the blood to clot. It became apparent that there was complete absence of fibrinogen in the patient's blood, and a supply of Fraction I (Cohn)¹⁰ was obtained (Fraction I contains the

*The Fraction I of normal human blood plasma used in this case was processed by the American National Red Cross from blood that it collected from voluntary donors. This material was prepared with the collaboration of the Department of Physical Chemistry, Harvard Medical School, and was furnished for civilian use without charge.

*From the Medical and Obstetrical Services, St. Elizabeth's Hospital.

†Visiting physician, St. Elizabeth's Hospital.

‡Assistant in surgery, St. Elizabeth's Hospital.

§Visiting obstetrician, St. Elizabeth's Hospital.

NITRATE METHEMOGLOBINEMIA

HAROLD MARCUS, M.D.,* AND JOY R. JOFFE, M.D.†

BROOKLYN AND NEW YORK CITY

MORE than forty years have passed since the first report of a fatal case of methemoglobinemia secondary to bismuth subnitrate ingestion.¹ Fifteen years ago Roe² reviewed the subject and re-emphasized the hazards attending its use. Nevertheless, during the past four years 3 more cases have been reported.³⁻⁵ A recent experience with a newborn infant has prompted us to review the general subject of nitrate methemoglobinemia, with emphasis on the causes, the types encountered, the mechanism involved and the rationale of present-day therapy.

Thirty cases of methemoglobinemia secondary to bismuth subnitrate, ammonium nitrate and nitrates in well water have been reported. The case reported below followed the ingestion of bismuth subnitrate on prescription.

We wish to point out that 4 of the 5 fatal cases of nitrate methemoglobinemia were in the group that followed bismuth subnitrate administration. Hence it is our opinion that still another warning to the medical profession regarding its use is indicated particularly in view of the rapidly favorable outcome following the application of accepted therapeutic procedures.

CLASSIFICATION OF METHEMOGLOBINEMIAS

Methemoglobinemia may occur during the course of various diseases or may follow the ingestion of a variety of toxic agents. A slight modification of Ferrant's⁶ classification is as follows:

Plasma methemoglobinemia In this variety the methemoglobin is formed in the plasma after the liberation of hemoglobin from the red blood cells by hemolysis. This may occur in blackwater fever, eclampsia, paroxysmal hemoglobinuria, anaerobic sepsis and Winckel's disease of the newborn.

Cellular methemoglobinemia In this variety hemoglobin, which contains iron in its ferrous form, is oxidized within the red blood cell by various agents to methemoglobin, which contains iron in its ferric form. This type is further subdivided into idiopathic or enterogenous — according to van den Bergh,⁷ nitrite is formed in the bowel from nitrate by nitrite-forming organisms and absorption is encouraged by a damaged intestinal mucosa — and toxic, which comprises the largest

and most important group of methemoglobinemias (the agents responsible include primarily the drugs containing nitro and amino groups, such as derivatives of aniline, certain sulfonamides, nitrates and nitrites³⁻¹⁰).

Our interest centers on the methemoglobinemias produced by nitrate ingestion.

REVIEW OF THE LITERATURE

According to Beck,¹¹ cases of bismuth subnitrate poisoning were reported as early as 1793, but impurities such as arsenic were thought to be responsible. Eusterman and Keith¹² cite Gamgee¹³ as the first to demonstrate in 1886 that amyl nitrite could produce methemoglobinemia. In 1906 Bennecke and Hoffmann¹ reported the first fatal case of methemoglobinemia following bismuth subnitrate ingestion. Shortly afterward, Böhm¹⁴ presented a report of a fatal case of methemoglobinemia following the administration of bismuth subnitrate by enema. He believed that intestinal putrefaction accelerated nitrite formation and rapid poisoning and stated that in fatal cases patients invariably suffered from intestinal disease. Thus, the danger of administration of bismuth subnitrate to infants, particularly when intestinal dysfunction existed, was established over forty years ago. Nowak and Gütig¹⁵ showed that adults were not immune to nitrite poisoning after bismuth subnitrate. In reviewing the literature, Beck,¹¹ in 1909, made the first concise contribution on the general subject of poisoning due to nitrate, though limiting himself to bismuth subnitrate.

Years later, Eusterman and Keith¹² reported 2 nonfatal cases of methemoglobinemia in adults following the administration of ammonium nitrate as a diuretic. In both cases there was evidence of intestinal dysfunction. Tarr¹⁶ collected 9 cases of methemoglobinemia following the ingestion of ammonium nitrate, of which he personally observed 4. In his cases renal impairment rather than intestinal dysfunction was the common denominator.

Roe,² in 1933, reported the fourth case of methemoglobinemia due to bismuth subnitrate ingestion and recommended the use of bismuth subcarbonate in its place for the treatment of diarrhea.

In the past few years a series of papers on methemoglobinemia due to the ingestion of well water of high nitrate content have appeared. Schwartz and Rector¹⁷ reported a case of idiopathic methemoglobinemia in an infant fed a powdered milk formula and living in the country. Comley,¹⁸ in describing 2 cases of this type, clarified the above

*Assistant physician, Maimonides Hospital, Israel Zion Division, assistant physician, Jewish Sanatorium and Hospital for Chronic Diseases, formerly resident in medicine, Meadowbrook Hospital, Hempstead, New York.

†Assistant resident, Chest Service, Bellevue Hospital, formerly resident in medicine, Meadowbrook Hospital, Meadowbrook, New York.

"plasminogen of normal blood is of a potential activity to destroy the total fibrinogen of normal blood in a few minutes" Plasmin is held in an inert form by an antifibrinolytic, antiplasmin. Plasmin can be activated by a variety of conditions, which either destroy antiplasmin or activate plasminogen. MacFarlane¹⁷ indicates that the mechanism of plasmin activation is obscure, and he states that it may be concerned with shock, tissue breakdown, blood coagulation and other phenomena.

Smith⁵ recently discovered in menstrual fluid a euglobulin that is both a vascular toxin and a fibrinolysin. Moreover, he extracted from the serum of toxemic and other patients a euglobulin with fibrinolytic activity similar to that found in menstrual discharge. In the hypothesis advanced, the source of the fibrinolytic factor is in the degenerating decidua, and the Smiths⁴ state that this tissue substance is akin to Menkin's "necrosin." Whether this fibrinolysin (or fibrinogenolysin) is a proteolytic enzyme released directly from tissue itself or whether there is an activation of fibrinolysin or an inhibition of antifibrinolysin remains to be determined. In any event, the work of the Smiths offers a new and promising approach to the problem of the etiology of toxemia of pregnancy, and it has shed light on the obscure and difficult subject of fibrinolysis in general.

It is apparent that the coagulative defect is not the whole story in this hemorrhagic diathesis. In the case reported above, there was severe vascular damage associated with spontaneous bleeding from mucous membranes and into the skin without evidence of thrombocytopenia. It has long been claimed that the toxin in toxemia of pregnancy acts on the blood vessels.¹⁸ The Smiths⁴ also state that the toxin from the decidua is a vascular toxin as well as a proteolytic enzyme. As suggested by Williams¹⁹ twenty-five years ago, there is a striking analogy between the activity of this type of toxin and certain snake venoms having toxic vascular and proteolytic effects.

From a practical standpoint, if similar cases are encountered, administration of large amounts of fibrinogen (as Fraction I, Cohn), to restore the coagulability of the blood and the rapid removal of the uterus with its presumably toxic contents, may be, as it seemed in the case reported above, a life-saving procedure.

SUMMARY AND CONCLUSIONS

A case of hemorrhagic diathesis in pregnancy with separation of the placenta is described. The patient had none of the usual manifestations of toxemia of pregnancy but had a bleeding disorder

characterized by spontaneous bleeding from the gums and into subcutaneous tissues and incoagulability of the blood.

Studies on the blood revealed a total lack of fibrinogen as the cause of the clotting defect.

Administration of a large amount of fibrinogen (Fraction I, Cohn) intravenously was followed by a return of the clotting time to normal, and removal of the uterus was accomplished, with recovery of the patient.

Suggestive evidence of a lack of an antifibrinogenolysin was noted in experiments carried out on the plasma of the patient. However, a definite fibrinolytic effect was not established in the serum, plasma or whole blood. The failure to demonstrate a fibrinolysin may have been due to technical difficulties and does not necessarily rule out the presence of this factor.

The concept of a toxin arising in the decidua capable of exerting a toxic effect on the blood vessels, as well as having a proteolytic activity, gains support in some measure from the findings in this case.

We are indebted to Drs. O. W. Smith, G. V. S. Smith and L. K. Diamond for their advice and help.

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of nitrate methemoglobinemia if no history of nitrate ingestion is obtainable, it is incumbent on the physician to ascertain whether or not well water of high nitrate content has been ingested, the cyanosis is described as an unusual grayish-brown color, the blood in methemoglobinemia is generally described as chocolate brown, brownish red or brownish black (hemolysis does not occur), blood transfusion frequently intensifies the cyanosis by enhancing the formation of additional methemoglobin, and chemical analysis of blood demonstrates nitrites

Therapeutic Rationale

A certain percentage of patients with minimal cyanosis and symptoms will recover without therapy after withdrawal of the toxic agent. Wallace,⁵ however, likens the methemoglobinemia following nitrate ingestion to the effects of rapid hemorrhage and that of enterogenous cyanosis and aniline poisoning to the effects of slow blood loss. The most urgent therapy is therefore required in cases of more advanced nitrate methemoglobinemia, and the critical period is the first twelve hours.

The treatment of choice in severe cases is the use of an agent that will hasten reconversion of methemoglobin to hemoglobin. Thionin and methylene blue are two such agents. Ascorbic acid and niacin possess the same property but act more slowly. Hence, they are more applicable to cases of methemoglobinemia due to aniline, sulfanilamide and plasmochin. Methylene blue catalyzes the physiologic reduction of methemoglobin by the body. According to Wendel,⁸ after administration in dilute solution, methylene blue is converted to the leuco or reduced form of dye by certain cellular enzymes in the red blood cell and other body cells. According to Hauschild,²⁹ who reported on the effectiveness of thionin and methylene blue (tetramethyl thionin hydrochloride) in the treatment of methemoglobinemia, a reversible oxidation-reduction system of thionin-leukothionin is produced initially. The hemoglobin-methemoglobin system is then shifted in favor of hemoglobin. Hauschild claimed that thionin administered intravenously was effective in ten minutes. Lederer³⁰ is quoted by Ferrant⁶ as follows: "Thionin, a non-toxic, violet dye, not methemoglobin formative, has a reducing power five times that of methylene blue." Thus, the use of thionin in place of methylene blue bears investigation.

At present a rapid though brief action may be expected after the intravenous injection of methylene blue. The accepted dosage is 1 or 2 mg per kilogram of body weight injected intravenously over a period of five minutes. An effect can be expected within thirty minutes. Injection of the dye under the skin and around the vein is painful and may produce necrosis. Furthermore, too rapid injection may produce hives and severe burning of the mouth. It must be emphasized again that the dye when used

intravenously produces a rapid but brief action. Hence, it is important to supplement with oral therapy for prolonged action. Ten times the intravenous dose should be given orally at the same time and repeated once or twice to cover the critical period of anoxia. It has, moreover, been suggested that glucose in vitro transforms methemoglobin into oxyhemoglobin. We have also mentioned the favorable influence of an alkaline medium. Hence, the utilization of glucose and sixth-molar lactate solutions after the intravenous administration of methylene blue appears to be desirable.

SUMMARY

The general subject of nitrate methemoglobinemia is reviewed.

A case of bismuth subnitrate methemoglobinemia recently encountered is presented.

The mechanisms involved in the formation of methemoglobin and in the evolution of rational therapy are discussed.

The increasing number of reports of methemoglobinemia due to nitrates in well water point to the growing importance of this variety.

It is re-emphasized that the use of bismuth subnitrate as a therapeutic agent is unnecessary, unwarranted and hazardous.

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syndrome and attributed the methemoglobinemia to the nitrates in well water. Additional cases were reported from Belgium by Ferrant,⁶ again from country communities in the United States by Faucett and Miller,¹⁹ Chapin²⁰ and Stafford²¹ and from Canada by Medovy, Guest and Victor.²²

CASE REPORT

D B, a 3-week-old infant with a birth weight of 4 lb, 9 oz, was discharged from the hospital on the 9th day on an Olac formula. At the age of 2 weeks he had attained a weight of 5 lb, 12 oz. Six days prior to admission diarrhea developed, and a change of formula was made. The diarrhea persisted, however, and bismuth subnitrate was administered in a compound prescription at the rate of 0.1 gm (1½ gr) every 3 or 4 hours. Medication was taken as ordered for 1 day but was withheld on the night prior to admission because of the patient's bluish color. On the following morning the color improved, and medication was resumed. That evening cyanosis became marked. The attending physician administered physiologic saline solution by hypodermoclysis and referred the patient to the hospital.

Physical examination revealed a grayish-blue cyanosis. The weight was 5 lb, 8 oz. The temperature was 98°F. Activity was normal, and there was no evidence of dehydration. The head and neck were essentially normal. The heart did not appear enlarged, its rate and rhythm were normal, and no murmurs were audible. The lungs were clear to percussion and auscultation. Except for phimosis the remainder of the examination was negative.

Urinalysis and a complete blood count were within normal limits. The blood was chocolate brown when the first specimen was drawn.

The admission diagnosis of methemoglobinemia was established after the initial withdrawal of blood for examination, though the etiology was not determined until the following day. Premature management was begun at once, and the infant was given a small blood transfusion and kept in an atmosphere of high oxygen concentration. Because respiratory difficulty was not marked, methylene blue therapy was withheld initially. This course was justified by the rapid improvement incident to the measures employed. Residual cyanosis was barely visible twelve hours after admission, and twenty-four hours after admission it had disappeared completely.

PRESENT CONCEPTS

Formation of Methemoglobin

Van den Bergh,⁷ writing on enterogenous cyanosis, stated that nitrates were converted into nitrite within the intestinal tract by bacteria, the nitrite being absorbed through the injured intestinal wall and recovered in the blood stream. Years later ZoBell²³ showed that many organisms found in the intestinal tract could change nitrate into nitrite in vitro. It is now generally hypothesized that, after the introduction of nitrate into the intestinal tract, there is normally a conversion of a portion of the nitrate into nitrite and ammonia. After absorption in greater or lesser amount, nitrite may react with hemoglobin or may be excreted by the kidney. The reaction of nitrite with hemoglobin results in the formation of methemoglobin by oxidation, ferrous ion being converted to ferric ion. The process is reversible, but reconversion to hemoglobin is slow, requiring a minimum of eight or nine hours, according to Wendel,²⁴ and longer according to other authors. Inasmuch as anoxia is the basis of the symptomatology, the crux of the problem lies in the

management of the patient during the first eight to twelve hours.

Before cyanosis due to methemoglobinemia occurs, a considerable amount of nitrite must be absorbed and retained in contact with hemoglobin. According to Wendel,⁸ methemoglobin should make up at least 10 per cent of the total blood pigment before cyanosis becomes visible. Miller⁴ quotes 3 gm of methemoglobin per 100 cc of blood as the critical figure for visible cyanosis.

Our review of the literature has uncovered many factors that play a part in the absorption of nitrite and its reaction with hemoglobin to form methemoglobin.

Chemical nature of the toxic agent It is generally recognized that methemoglobinemia appears more quickly after nitrate ingestion than after sulfanilamide or plasmochin.⁸

Age of patient Infants are more susceptible because of the greater frequency of gastrointestinal disturbances, the presence of a bacterial flora more favorable to nitrite production (Böhme,¹⁴) the existence of nitrate-splitting organisms high in the intestinal tract, which would facilitate the reduction of the nitrate to nitrites before the nitrate could be completely absorbed,²⁵ and possibly because of less renal efficiency in eliminating nitrites.

Mode of administration of nitrate It has long been recognized that a more severe and prompt methemoglobinemia results from the rectal administration of nitrate (Böhme¹⁴).

Integrity of intestinal mucosa Van den Bergh⁷ implicated the injured intestinal mucosa as a factor many years ago.

Amount of nitrate administered The appearance of cyanosis due to methemoglobinemia is generally dependent on the amount of nitrate ingested. This was recognized by Böhme¹⁴ years ago, and substantiated by the cases of Barker and O'Hare²⁶ and Tarr.¹⁶

Renal status Nitrite retention on the basis of renal insufficiency has been implicated by Tarr.¹⁶

Rapidity of passage through the intestinal tract Incomplete reduction of nitrate to ammonia may be the result of rapid passage through the intestine with the intermediate nitrite present in greater quantity near the absorbing surface of the intestine.

pH of blood Greenberg et al.²⁷ have shown that the conversion of hemoglobin to methemoglobin in the presence of nitrite occurs more rapidly in an acid medium. Furthermore, Marshall and Marshall²⁸ lessened the symptoms of nitrite poisoning experimentally by intravenous administration of sodium carbonate or bicarbonate.

Diagnosis of Methemoglobinemia

The diagnosis of methemoglobinemia with scientific certainty is made only by spectroscope or spectrograph. The average physician, however, will rely on the following points to establish a diagnosis

of nitrate methemoglobinemia if no history of nitrate ingestion is obtainable, it is incumbent on the physician to ascertain whether or not well water of high nitrate content has been ingested, the cyanosis is described as an unusual grayish-brown color, the blood in methemoglobinemia is generally described as chocolate brown, brownish red or brownish black (hemolysis does not occur), blood transfusion frequently intensifies the cyanosis by enhancing the formation of additional methemoglobin, and chemical analysis of blood demonstrates nitrites

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It is re-emphasized that the use of bismuth subnitrate as a therapeutic agent is unnecessary, unwarranted and hazardous.

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STREPTOMYCIN IN THE TREATMENT OF SALMONELLA ENTERITIS IN INFANTS*

SIDNEY ROSS, M D,† FREDERIC G BURKE, M D,‡ E CLARENCE RICE, M D,§
HAROLD BISCHOFF, M D,¶ AND JOHN A WASHINGTON, M D ||

WASHINGTON, D C

THE susceptibility of various strains of salmonella in vitro to streptomycin has been adequately demonstrated by West et al¹ However, the clinical efficacy of this antibiotic in salmonella enteritis has not been too extensively investigated, and relatively few cases have been reported thus far among children Seligmann et al² used strepto-

dose of streptomycin was used in Seligmann's series, ranging between 0.2 and 0.8 gm a day for three or four days In 1 case, combined oral and intramuscular administration was used and similarly failed to effect a permanent cure Swiller and his associates,³ on the other hand, reported a bacteriologic cure of an eight-month-old salmonella car-

TABLE 1 Summary of 8 Cases of Salmonella Enteritis Treated with Streptomycin

CASE No	AGE	ETIOLOGIC ORGANISM	STREPTOMYCIN SENSITIVITY BEFORE TREATMENT	STREPTOMYCIN SENSITIVITY AFTER RELAPSE	DOSE OF STREPTOMYCIN	
					ORAL	INTRAMUSCULAR
	mo		unit/cc	unit/cc		
1	15	<i>S. manhattan</i>	5.0	5.0	0.4 gm. every 4 hr. for 7 days 0.8 gm. every 4 hr. for 8 days.	None
2	3	<i>S. typhimurium</i>	5.0	5.0	0.4 gm. every 4 hr.	None
3	36	<i>S. oranienberg</i>	10.0	10.0	0.6 gm. every 3 hr.	0.1 gm. every 6 hr.
4	5	<i>S. typhimurium</i>	4.0	5.0	0.1 gm. every 4 hr.	None
5	4	<i>S. anatis</i>	12.5	—*	0.4 gm. every 4 hr.	0.1 gm. every 6 hr.
6	9	<i>S. meunchen</i>	10.0	7.5	0.4 gm. every 4 hr.	0.1 gm. every 6 hr.
7	1	<i>S. oranienberg</i>	10.0	12.5	0.4 gm. every 4 hr.	0.15 gm. every 8 hr.
8	8	<i>S. typhimurium</i>	6.0	7.5	0.6 gm. every 4 hr.	0.2 gm. every 8 hr.

*No relapse

mycin in 5 cases of enteritis due to *Salmonella typhimurium* in the newborn period and observed only a transitory sterilization of the bowel, and in all 5 cases the pathogenic organism reappeared in the stool, usually within forty-eight hours after the drug had been discontinued. A relatively small oral

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†Instructor in pediatrics, George Washington University School of Medicine; research fellow, National Institute of Health; junior attending physician, Children's Hospital.
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rier when 1 gm. of streptomycin was given orally daily for twenty consecutive days. Pulaski and Amspacher⁴ treated 3 cases of salmonella enteritis in infants, using a daily oral dose of 100 mg. per kilogram of body weight for four to seven days, and the stool cultures became negative and remained so during a three-week follow-up period. Except for these three reports, the literature on the treatment of salmonella enteritis in infancy with streptomycin has been limited.

During the past year, we have had the opportunity of treating 8 patients, ranging in age from three months to three years, with large doses of streptomycin for a prolonged interval. This report deals with the clinical and bacteriologic observations made in these cases.

BACTERIOLOGY

Rectal swabs were obtained daily and immediately streaked by the bedside on salmonella-shigella (SS) agar and desoxycholate citrate (DC) and incubated for twenty-four hours. In addition, Kauffmann's tetrathionate broth was seeded with the rectal swab and subcultured on SS plates after eighteen to twenty-four hours of incubation. Colorless colonies from SS and DC mediums were subcultured into Kligler's iron agar and identification of the organisms was performed with the use of type-specific H serums*. In questionable cultures, sugar broths, examination for motility, indole formation and other biochemical identification procedures were employed. The distribution of the various types of salmonella in this series was as follows: *S. typhimurium*, 3 cases, *S. oranienberg*, 2 cases, and *S. meunchen*, *S. manhattan* and *S. anatis*, 1 case each.

It is worth while to emphasize the desirability of repeated stool-culture examinations both for diag-

droxamine hydrochloride on the coliform inhibitory properties of the mediums itself, and this procedure was therefore abandoned.

It is well to point out that tetrathionate broth proved to be the most sensitive medium in the isolation of salmonella organisms in our 8 cases. A total of 160 stool cultures were obtained in this series (an average of 20 per patient), of which 78 were positive for salmonella. Of these, 73 specimens yielded salmonella in tetrathionate broth, 42 on desoxycholate citrate agar, and 39 on SS agar. In the majority of cultures, the organism was recovered from two or all three mediums simultaneously. In 33 out of 78 positive cultures, however, salmonella was isolated from only one culture medium. Tetrathionate broth exclusively yielded a positive culture in 28 cases, whereas positive cultures were isolated solely on SS agar in 3 specimens and desoxycholate citrate in 2. This serves to emphasize the desirability of culturing stools on all three mediums simultaneously, in view of the fact that no single medium yielded salmonella on all

TABLE 1 (Continued)

CASE NO	DURATION OF TREATMENT	TOTAL DOSE OF STREPTOMYCIN		OUTCOME	COMMENT
		ORAL gm.	INTRAMUSCULAR gm.		
1	days 15	57.6	None	Recurrence	Stool cultures positive throughout streptomycin therapy
2	12	30.4	None	Recurrence	Stool cultures negative during therapy; recurrence of positive cultures 6 days after streptomycin discontinued.
3	11	37.2	4.1	Recurrence	Stool cultures negative during therapy; recurrence of positive culture 8 days after streptomycin discontinued.
4	8	4.8	None	Recurrence	Stool cultures negative during therapy; recurrence of positive culture 5 days after streptomycin discontinued.
5	10	24	4	Cure	Stool cultures negative during therapy; still negative after 1 mo. follow up study.
6	14	33.6	5.6	Recurrence	Stool cultures negative during therapy; recurrence of positive culture 3 days after streptomycin discontinued.
7	11	26.4	4.9	Recurrence	Stool cultures negative during therapy; recurrence of positive culture 5 days after streptomycin discontinued.
8	14	50.4	8.4	Recurrence	Majority of stool cultures positive during streptomycin therapy.

nosis and for follow-up purposes even with the selective mediums now available. The latter permit the detection of a small number of pathogens in feces by substantially inhibiting the coliform group. However, unless repeated stool examinations are performed during and after treatment with streptomycin, abortive "cures" may be reported.

Hydroxamine hydrochloride (1:300), adjusted to a pH of 6.0, was incorporated in some control SS plates in an attempt to neutralize the inhibitory effect of the streptomycin excreted in the stool. However, the plates showed definite overgrowth with *Escherichia coli*, indicating a vitiating effect of hy-

positive stool specimens. If only one medium is to be seeded at the bedside for follow-up purposes in cases of proved salmonella infection, tetrathionate broth would undoubtedly be the most useful one to use.

DOSAGE AND MODE OF ADMINISTRATION OF STREPTOMYCIN

The lack of response of salmonella infections to smaller doses of streptomycin in Seligmann's series prompted us to use a considerably larger dosage ranging from 0.8 to 4.8 gm. a day orally, with an average of 2.4 gm. daily. The drug† was administered for an interval ranging between eight and

*We are indebted to Dr. Erich Seligmann, of the National Salmonella Typing Center, New York, and to Drs. H. Carlquist and L. R. Kuhn of the Army Medical Center, Washington, D. C. for confirmation and final identification of the organism by the use of group-specific O serums.

†Kindly supplied as syrup of streptomycin (50 mg. per cubic centimeter) by E. R. Squibb and Sons. This preparation was readily accepted and well tolerated by all the patients.

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7	1	<i>S. oranienberg</i>	10 0	12 5	0.4 gm. every 4 hr.	0.15 gm. every 8 hr.
8	8	<i>S. typhimurium</i>	6 0	7 5	0.6 gm. every 4 hr.	0.2 gm. every 8 hr.

*No relapse

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‡Associate clinical professor Georgetown University School of Medicine associate clinical professor George Washington University School of Medicine director of pediatric instruction Children's Hospital

§Pathologist, Children's Hospital

¶Research fellow National Institutes of Health resident, Children's Hospital

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MEDICAL PROGRESS

SURGERY IN CHRONIC ARTHRITIS

JOHN G. KUHN, M.D.*

BOSTON

SURGERY is employed in chronic arthritis primarily to remove or to decrease deformities and disabilities that have occurred within and about the joints.¹ If adequate early medical and orthopedic care is given, almost all disability can be prevented in chronic arthritis, and much later surgery can be avoided.² If the joints that show swelling, muscular spasm and pain are splinted to relieve muscular spasm, in a position as near to full extension as they can comfortably be placed, and if flexion deformity is then prevented by a part-time maintenance of this position, little deformity will develop. Weakness in the supporting musculature must be prevented by exercise and other physiotherapy. Severe crippling is usually found in the patient when these simple measures have been neglected.³

In the preceding decade attempts were made through surgical measures to cure the arthritis or to alter certain physiologic disturbances. Among the surgical measures sympathectomy⁴ for the lower extremity and parathyroidectomy⁵ were most widely discussed. For the most part the early discussions of these procedures were optimistic, but later reports were more critical and disappointing.^{6,7} Old measures were discarded and forgotten, and new ones were enthusiastically accepted every year.⁸ One procedure that is still vigorously defended⁹ — and as strongly condemned as valueless¹⁰ — is the extensive removal of so-called foci of infection. This subject was recently reviewed by Freyberg,¹¹ who concluded that if the arthritis was infectious a localized infection might be a trigger mechanism that started it. Removal of foci of infection was probably of no value in rheumatoid arthritis of long duration. Foci of infection should be attacked only as part of a broad program of treatment.

The aims of surgery in chronic arthritis are outlined by Wilson.¹² He speaks of the value of partial rehabilitation through well thought out surgical procedures followed by prolonged physiotherapy. In a similar manner Fisher¹³ states that orthopedic surgery can often prevent deformity in chronic arthritis, can correct deformity sometimes, can always improve function and can alleviate pain.

No surgical measures should be undertaken unless there is reasonable assurance that they will decrease pain or improve function. The usual indications and

contraindications were outlined succinctly fifteen years ago by Wilson and Osgood.¹⁴ The indications and contraindications need little modification. Quiescence of the arthritis, optimal general condition and good morale of the patient, adequate facilities for hospitalization and follow-up care. The patient should be emotionally stable and co-operative, with a sincere desire to get well. In most cases the operation is but one step in the restoration of articular function, rarely is function restored by the operative procedure alone. Before operation there should be several weeks of muscular re-education or at least muscle-setting exercises to teach the patient to use, as well as to strengthen, the muscles that will later move the joint or the limb.¹⁵ Operative procedures are usually valueless unless there is sufficient muscular strength obtainable to make useful function possible later. After operation a prolonged period of physiotherapy and exercises is required to get the greatest possible benefit. The surgeon should have a definite plan of rehabilitation. Usually, deformities in the upper extremity are treated before those in the lower extremity.

Surgical procedures are generally not contemplated in the treatment of chronic arthritis until one has clinical and laboratory evidence that the disease is quiescent.¹⁶ Most surgeons state that the patients have a more rapid convalescence, with fewer complications, and that exacerbations in the arthritis are much less likely to occur if surgery is delayed until the disease has become quiescent.^{17,18} It has been suggested that surgical procedures may be performed more easily if one does not wait for complete healing and quiescence of the arthritis.¹⁹ Although operation can be carried out with greater ease before bony ankylosis and severe contractures have occurred, if the disease is still active the convalescence is prolonged and a recrudescence of acute arthritis is often observed.²⁰ Moreover, after the inflammation in the joint subsides, a remarkable spontaneous improvement in function is sometimes seen. Unnecessarily radical procedures may be performed if one does not wait for the unaided recovery of function that follows quiescence of the disease. In rare cases operation is necessary in the early, acute stage of the arthritis, particularly when adduction deformity is present in both hips, to give the patient comfort or to make nursing care possible.²¹

*Instructor in orthopedic surgery, Harvard Medical School; lecturer in orthopedic surgery, Boston University School of Medicine; chief of surgical and orthopedic staffs, Robert Breck Brigham Hospital.

fifteen days, with an average of eleven and three-fifths days per patient. Each patient received an average of 28 gm of streptomycin orally during the course of therapy. In spite of these large doses, spot blood assays during treatment showed no detectable level of the drug when the oral mode of administration was used exclusively. This is in keeping with the well known fact that streptomycin is not absorbed from the intestinal tract. In 5 of the 8 cases in our series, streptomycin was simultaneously administered intramuscularly in a dose ranging between 0.4 and 0.6 gm a day.

RESULTS

The pertinent data on the eight cases are presented in Table 1. It will be noted that only 1 patient in this series (Case 6) showed salmonella to be permanently absent from the stool cultures. This infant received both oral and intramuscular streptomycin. In 6 other cases a definite inhibitory effect on both the salmonella organisms and the normal stool flora was observed during the period of drug administration, however, in spite of the large doses used, the pathogen reappeared in the stool three to eight days after discontinuation of the drug. In Case 1, in which the strain proved to be *S. manhattan*, the patient continued to have positive stool cultures throughout the course of therapy, even when 4.8 gm of streptomycin a day was administered orally. In 4 of the 5 patients who received combined oral and intramuscular streptomycin, there did not appear to be any enhancement in the efficacy of therapy or any noticeable delay in the reappearance of the salmonella organisms. It thus appeared that combined oral and parenteral administration of streptomycin was no more effective than oral administration alone. In view of the small number of cases in this series, it was not possible to say whether any particular strain of salmonella showed any significant variation in response to streptomycin therapy. None seemed to be apparent except perhaps for the undue bacteriologic refractoriness of the patient with the manhattan strain of salmonella.

It is to be noted that the streptomycin sensitivities observed in this series ranged from 4.0 to 12.5 microgm per cubic centimeter prior to institution of streptomycin therapy. Of interest was the observation that in no case was any significant increase in streptomycin resistance noted when the pathogen reappeared in the stools after termination of therapy. Thus, the failure of streptomycin in salmonella enteritis can hardly be explained on the basis of acquired resistance of the organism. Nor can it be explained on the basis of the initial resistance of salmonella since a sensitivity of 4.0 to 12.5 microgm per cubic centimeter would place the salmonella among the relatively sensitive groups of organisms susceptible to streptomycin. Experi-

mental studies on streptomycin stool levels obtained after the administration of varying doses of the drug orally to infants have been conducted in our laboratory during the past several months, and it has been found that with doses ranging from 0.2 to 0.4 gm every four hours, the streptomycin stool levels ranged between 10,000 and 20,000 microgm per gram of dried feces. To a first approximation, this was the dosage used in the present series of salmonella enteritis. Thus, the sensitivity of the salmonella organisms in these 8 cases was exceeded 1000 to 5000 times in streptomycin stool concentration, and yet streptomycin therapy was singularly disappointing. An analogous situation obtains in typhoid fever, in which streptomycin has been demonstrated to produce a marked inhibitory action against *Eberthella typhosa* in vitro and yet clinically and bacteriologically the antibiotic exerts no salutary effect against typhoid fever in human beings.

All 8 children showed an uneventful clinical improvement and were discharged from the hospital in good condition. Whether any favorable clinical effect was exerted by streptomycin on the course of the disease in this series is problematic. Only 3 of the 8 cases showed any marked constitutional symptoms at the time of admission, characterized by high fever, toxicity, acidosis and dehydration. It is not unlikely that vigorous management of these symptoms per se was the significant factor in effecting a favorable outcome.

SUMMARY

Eight cases of salmonella enteritis in infants and children were treated with streptomycin in large doses. Three of the patients received the drug orally alone, whereas the other 5 were given the antibiotic both orally and intramuscularly.

In spite of the demonstrated susceptibility of the salmonella organism to streptomycin in each case, only 1 of the 8 patients was rendered permanently free of salmonella. In the other 7, an inhibitory effect on both the salmonella organisms and the normal stool flora was observed during the period of drug administration, however, three to eight days after streptomycin had been discontinued, the pathogen reappeared in the stools. No significant increase in streptomycin resistance was noted in any case.

We are indebted to Miss Sara Stevens, Mrs. Eleanor Weinstein and Miss Susan Gougé for their technical assistance.

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olar side of the capsule at the interphalangeal joints permits full extension at these joints⁴³ At the hip, when flexion is present, section of the fascia lata in the upper third of the thigh is occasionally useful

In the popliteal space and occasionally at the sides of the interphalangeal joints an outpouching or herniation of a part of the articular capsule may appear Such swellings are usually herniations of the joint, which at the knee are sometimes called Baker's cysts⁴⁴ Occasionally these swellings subside spontaneously or decrease with pressure dressings If they persist or become larger, their removal is indicated It has been suggested that some of them may be enlarged bursas at the back of the knee⁴⁵ The treatment usually advocated is simple removal of the sac, with overlapping of the fascia or muscles across the origin of the herniation from the articular capsule Similarly, rheumatic nodules, which appear on the extensor surface of the bones in about 20 per cent of patients with rheumatoid arthritis, sometimes become irritated and painful When pressure comes continually upon such an area, the rheumatic nodule should be removed

When there is persistent painful swelling of the articular capsule from excessive formation of synovial fluid, aspiration and the application of a pressure dressing are usually advised Opinion is divided about the value of repeated aspirations either for diagnosis or for therapy⁴⁶ Usually, only temporary relief is given Continued hydrarthrosis at a joint is generally evidence of chronic irritation within the articular cavity⁴⁷ If clinical or x-ray examination shows any internal derangement, a foreign body, a displaced meniscus or greatly thickened synovial tissue, an arthrotomy with the removal of the tissue causing the irritation is indicated The articular capsule is opened through the front or back of the joint, depending upon the position of the irritating material After removal, the hydrarthrosis usually ceases

Synovectomy — the removal of a portion or all of the synovial membrane — still has no established indications in rheumatoid arthritis⁴⁸ Its value has been recognized since its early description by Swett⁴⁹ The synovial membrane is no longer removed under the mistaken idea that it may be a focus of infection The chief indication in rheumatoid arthritis is mechanical interference with function⁵⁰ If the swelling and thickening of the synovial membrane have been present less than a year, treatment with deep x-ray therapy may cause them to subside⁵¹ In massive swelling that is resistant to x-ray therapy or has been present for a long time synovectomy is generally required The usual technique is to remove the synovial membrane as completely as possible through a long parapatellar incision No tourniquet is used, but hemostasis is controlled with the electrocautery⁵² Degenerated semilunar cartilages and interarticular ligaments must usually be removed also at the knee joint Partial synovectomy is sometimes required at the

elbow joint when the thickened tissue interferes with extension Removal of the synovial membrane on both sides of the olecranon and from the olecranon fossa is usually adequate Adhesions form quickly after synovectomy if motion cannot be started soon and usually account for most of the poor results⁵³ Cellophane and thin nylon membrane have been used over the suprapatellar space with some benefit to prevent adhesions after synovectomy⁵⁴ Where there is great destruction of the articular cartilages in addition to the thickened synovial membrane, synovectomy is usually not helpful, arthroplasty or arthrodesis is generally advocated

Osteotomy — the cutting of a bone to provide a better position for function — is indicated occasionally in the treatment of arthritis⁵⁵ When a joint is stiff the surgeon must decide whether function will be served better by the formation of a new joint or by leaving the joint stiff, with the limb placed in the best position for function At the wrist and finger joints, and usually at the tarsal joints, a stiff joint in a good position is considered to be the most satisfactory procedure When the wrist joint has been destroyed, osteotomy is advocated followed by fusion in about 30° of dorsiflexion At the interphalangeal joints when the joint is ankylosed or seriously deformed, osteotomy is carried out through the joint After osteotomy the joint is held in 30 to 40° of flexion with fine Kirschner wire until the joint becomes solidly fused⁵⁶ This gives a much more useful finger than an arthroplasty, which always causes lateral instability at the interphalangeal joints Osteotomy has been mentioned at the metacarpophalangeal joint to correct severe subluxation and ulnar deviation Here the distal end of the metacarpal bone is trimmed off squarely Occasionally the proximal end of the proximal phalanx must be also reshaped⁵⁷ Resection of the outer part of the acromion — "acromioplasty" — has been advocated to lessen pain and improve motion at the limited arthritic shoulder joint.¹⁹ Improved motion and lessening of pain at this joint have been reported

During the past few years attempts have been made to correct the fixed anterior bowing of the spine by osteotomy⁵⁷ Osteotomy is performed in the lumbar spine to improve the position of the dorsal and cervical regions of the spine in anterior flexion This is a very common late deformity in rheumatoid spondylitis Osteotomy is usually performed through the pedicles and articular facets in the lumbar region The lumbar spine is then hyperextended, and a surgical fusion is performed to hold the lumbar spine permanently in this position⁵⁸ Several varying surgical techniques have been reported⁵⁹

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The avowed purposes of surgical treatment in chronic arthritis have been given as follows²² to make a diagnosis, to relieve pain, to correct or to improve a deformity, and to obtain motion in a stiff joint. Usually, diagnosis is certain long before operation is contemplated. When there are unusual features or if tuberculosis is suspected, examination of articular tissues²³ or occasionally of regional lymph nodes, may be of value²⁴. Sometimes in monarticular arthritis when there is little change and no progression to other joints, arthrotomy with pathological examination of articular tissue may be necessary for the making of a diagnosis²⁵.

Operations and other procedures to relieve pain are palliative only. They do not influence the course of the arthritis or improve the impaired function. Yet they are at times most welcome to the sufferer from constant pain in the joints. Such procedures consist chiefly of injections about major nerves or into the periarticular tissues about an affected joint²⁶. Rarely are sensory nerves that supply the joint cut. Occasionally, the surgical stiffening of a painful joint is carried out, pain being relieved by the stopping of all motion²⁷.

Most surgical treatment in chronic arthritis is carried out for the correction of deformities. Manipulations, lengthening of contracted soft tissues and osteotomies are the procedures that are most frequently employed²⁸. Less than 5 per cent of the cases of rheumatoid arthritis progress to the ankylosis of joints, some degree of articular damage is the usual end result. The procedures available to improve motion in a stiffened joint are osteotomy, arthroplasty and resection²⁹. Although the surgical indications for the correction of disabilities in both rheumatoid arthritis and osteoarthritis are similar, it is better for the sake of clarity to review them separately.

RHEUMATOID ARTHRITIS

Manipulation — the stretching of contracted soft tissues about a joint with the patient anesthetized — has been discussed frequently³⁰. According to Lloyd Williams,³¹ it is of value in quiescent disease to correct mild deformity and to increase motion by stretching or rupturing adhesions and by stretching shortened muscles and fascia. It should be employed with caution in quiescent disease. It may light up a quiescent inflammation³². Because the bones in chronic arthritis do not have normal strength and break easily, great care must be exercised in carrying out manipulations³³. The usual technic is to bring the distal portion of the limb first into greater flexion and then to extend it slowly. If full correction is considered unwise at the first attempt, the manipulation can be repeated as soon as the soreness caused by the first manipulation has subsided. After manipulation the limb is held in the improved position for several days, and then physiotherapy is resumed³⁴. If no correction follows one manipulation, further

ones will be ineffective, and operative lengthening of the tight structures must usually be performed³⁵.

When soft tissues are so tight that no improvement follows corrective casts or manipulation, two useful procedures have been described for the correction of contracted soft tissues. These can be employed most effectively at the knee, and less well at the elbow or finger joints. When major surgery is considered hazardous and when there is not a great amount of bony atrophy, the contracted tissues can be stretched safely by turnbuckles attached to Kirschner wire. The Kirschner wires are drilled through the bones on the proximal and distal sides of the joint. By turning of the turnbuckles the articular surfaces are distracted, and the contractures are slowly stretched³⁶. The entire limb is usually kept in a posterior cast or in balanced traction for comfort. By this method relatively painless correction of flexion and of subluxation can be obtained in two or three weeks. This method cannot be used when the bones are extremely atrophied, for the wires will then be pushed through the bones. No pressure sores develop, nor is there extensive interfascial fibrosis, both of which are found with wedging casts and forcing apparatus. After correction has been obtained, the limb is put in a bivalved cast and physiotherapy is begun.

Immediate correction of resistant contractures in rheumatoid arthritis can be obtained by lengthening the tendons of the tight muscles and by freeing the posterior portion of the articular capsule if the general condition of the patient permits a major surgical procedure³⁷. A number of technics have been described since the early description of Silver³⁸. The simplest and most effective is that described by Wilson³⁹. The essential features of this operation are cutting of the iliotibial band and fascia lata, lengthening of the biceps femoris tendon and freeing of the posterior portion of the articular capsule. The leg is held in full extension until healing is well advanced, when active exercises are given. Walking with support is permitted in two or three weeks. When full, immediate motion of the flexion deformity stretches the popliteal vessel too much, extension is carried out gradually with changes of casts at weekly intervals. In this way there is no circulatory embarrassment in the foot, and no injury occurs to the common peroneal nerve. When the motion in the knee joint is quite limited, with considerable articular destruction, rotation osteotomy performed just above the condyles of the femur has been advocated⁴⁰. The disadvantage of this procedure is that much stiffness develops in the muscles and fascia while the osteotomy is healing, before movement can again be started in the knee⁴¹.

At the elbow joint a permanent flexion deformity can be improved by lengthening the expansions of the biceps tendon⁴². The flexion deformity at the elbow is usually not a serious disability, and operation is not often required. In the fingers, freeing the

ular side of the capsule at the interphalangeal joints permits full extension at these joints.⁴² At the hip, when flexion is present, section of the fascia lata in the upper third of the thigh is occasionally useful.

In the popliteal space and occasionally at the sides of the interphalangeal joints an outpouching or herniation of a part of the articular capsule may appear. Such swellings are usually herniations of the joint, which at the knee are sometimes called Baker's cysts.⁴⁴ Occasionally these swellings subside spontaneously or decrease with pressure dressings. If they persist or become larger, their removal is indicated. It has been suggested that some of them may be enlarged bursas at the back of the knee.⁴⁵ The treatment usually advocated is simple removal of the sac, with overlapping of the fascia or muscles across the origin of the herniation from the articular capsule. Similarly, rheumatic nodules, which appear on the extensor surface of the bones in about 20 per cent of patients with rheumatoid arthritis, sometimes become irritated and painful. When pressure comes continually upon such an area, the rheumatic nodule should be removed.

When there is persistent painful swelling of the articular capsule from excessive formation of synovial fluid, aspiration and the application of a pressure dressing are usually advised. Opinion is divided about the value of repeated aspirations either for diagnosis or for therapy.⁴⁶ Usually, only temporary relief is given. Continued hyarthrosis at a joint is generally evidence of chronic irritation within the articular cavity.⁴⁷ If clinical or x-ray examination shows any internal derangement, a foreign body, a displaced meniscus or greatly thickened synovial tissue, an arthrotomy with the removal of the tissue causing the irritation is indicated. The articular capsule is opened through the front or back of the joint, depending upon the position of the irritating material. After removal, the hyarthrosis usually ceases.

Synovectomy — the removal of a portion or all of the synovial membrane — still has no established indications in rheumatoid arthritis.⁴⁸ Its value has been recognized since its early description by Swett.⁴⁹ The synovial membrane is no longer removed under the mistaken idea that it may be a focus of infection. The chief indication in rheumatoid arthritis is mechanical interference with function.⁵⁰ If the swelling and thickening of the synovial membrane have been present less than a year, treatment with deep x-ray therapy may cause them to subside.⁵¹ In massive swelling that is resistant to x-ray therapy or has been present for a long time synovectomy is generally required. The usual technique is to remove the synovial membrane as completely as possible through a long parapatellar incision. No tourniquet is used, but hemostasis is controlled with the electrocautery.⁵² Degenerated semilunar cartilages and interarticular ligaments must usually be removed also at the knee joint. Partial synovectomy is sometimes required at the

elbow joint when the thickened tissue interferes with extension. Removal of the synovial membrane on both sides of the olecranon and from the olecranon fossa is usually adequate. Adhesions form quickly after synovectomy if motion cannot be started soon and usually account for most of the poor results.⁵³ Cellophane and thin nylon membrane have been used over the suprapatellar space with some benefit to prevent adhesions after synovectomy.⁵⁴ Where there is great destruction of the articular cartilages in addition to the thickened synovial membrane, synovectomy is usually not helpful, arthroplasty or arthrodesis is generally advocated.

Osteotomy — the cutting of a bone to provide a better position for function — is indicated occasionally in the treatment of arthritis.⁵⁵ When a joint is stiff the surgeon must decide whether function will be served better by the formation of a new joint or by leaving the joint stiff, with the limb placed in the best position for function. At the wrist and finger joints, and usually at the tarsal joints, a stiff joint in a good position is considered to be the most satisfactory procedure. When the wrist joint has been destroyed, osteotomy is advocated followed by fusion in about 30° of dorsiflexion. At the interphalangeal joints when the joint is ankylosed or seriously deformed, osteotomy is carried out through the joint. After osteotomy the joint is held in 30 to 40° of flexion with fine Kirschner wire until the joint becomes solidly fused.⁵⁶ This gives a much more useful finger than an arthroplasty, which always causes lateral instability at the interphalangeal joints. Osteotomy has been mentioned at the metacarpophalangeal joint to correct severe subluxation and ulnar deviation. Here the distal end of the metacarpal bone is trimmed off squarely. Occasionally the proximal end of the proximal phalanx must be also reshaped.⁴⁴ Resection of the outer part of the acromion — "acromioplasty" — has been advocated to lessen pain and improve motion at the limited arthritic shoulder joint.¹⁹ Improved motion and lessening of pain at this joint have been reported.

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Arthrodesis, the operative fusion of a joint in a useful position, is rarely employed in the treatment of rheumatoid arthritis. When a joint is severely damaged the natural tendency of the disease is to heal the lesion with fibrous or bony ankylosis of the

joint. When this ankylosis is unsound, arthrodesis may be indicated.⁶⁰ But most patients prefer either the use of apparatus to avoid pain or an operative procedure that will leave them with motion at the joint.^{61 62} Arthrodesis is justified as a temporary expedient to relieve pain rapidly at the knee or hip joint. This is performed by the use of nails or wire driven across the joint. Such immobilizing material can later be removed, and an operation to obtain motion can be performed when the arthritis becomes quiescent. In many cases, after arthrodesis, more arthritis and sprain have been observed in the joints above and below the arthrodesis. In the foot, arthrodesis of the tarsal joints and of the ankle joint in the best position for walking are useful procedures when these joints are hopelessly damaged and cause pain.⁶³ Usually, nature fuses these joints in the course of the arthritis and the surgeon's task is to keep the foot in good weight-bearing position until fusion takes place. For deformities in the anterior portion of the foot the procedures used for the treatment of severe static deformities are advocated.

Arthroplasty — the formation of a new, movable joint after ankylosis from rheumatoid arthritis — has been called the essence of patchwork surgery. Well fitting articular surfaces can be formed without difficulty in the major joints, but the bones frequently do not remain as they had been shaped.⁶⁴ The osteoporotic bones and the atrophied muscles, which are frequently found in the later stages of rheumatoid arthritis, are poor materials to work with. With weight bearing and with motion the ends of the bones often become greatly distorted. This distortion is much less when plastic or metallic molds are fitted over the articular surfaces.⁶⁵ Orthopedic procedures have been reported in most of the major joints, but useful joints, after arthroplasty, have been reported chiefly at the elbow, the hip and the knee.

At the elbow joint a number of procedures have been described from wide resection to arthroplastic procedures. All these procedures usually give a movable elbow joint, but an arthroplasty gives a somewhat more stable elbow.⁶⁶ Usually, fascia lata is interposed between the bone ends. A wide range of painless motion is reported, but normal strength and stability are not regained. At the knee joint, fascia has also been used as an interposition material to prevent reankylosis after arthroplasty. In most cases this has worn away quickly, but a small number of good results have been reported.⁶⁷ Cellophane and nylon membrane have been employed in a few cases, with somewhat greater success.²¹ In most cases a limited range of motion has been obtained after prolonged physiotherapy. Samson⁶⁸ believes that arthroplasty of the knee should be performed only rarely in rheumatoid arthritis.

At the hip joint when ankylosis has taken place arthroplasty is indicated when the patient must sit

for work. In persons who must stand, a stiff, painless hip in a good position for weight bearing is usually more satisfactory. Some satisfactory arthroplasties were obtained by the use of fat or fascia as interposition materials, but in most cases these substances quickly degenerated under pressure and reankylosis occurred.⁶⁹ Metallic or plastic cups that fit over the femoral head have withstood distortion and have given much more useful hip joints.⁷⁰

Arthroplasties have been reported on practically all the major joints of the body. A number of operations on the fingers and toes have been described. But for the most part, except for the elbow, the hip and the knee, these offer little gain in function. Rarely is arthroplasty required at the temporomandibular joint, ankylosis here is rare but some limitation of motion is common.⁷¹ A number of successful arthroplasties on this joint have been reported.

OSTEOARTHRITIS

Osteoarthritis rarely produces serious deformity, and, consequently, does not require surgical treatment very often. However, in persons who do heavy labor and in others with some malformation in a weight-bearing joint, severe pain and deformity are sometimes seen with osteoarthritis. Operation is performed more often for the relief of pain than for any other reason in osteoarthritis. Although most persons who seek surgical treatment are past middle age they stand surgical procedures surprisingly well. The indications and prerequisites are the same as those for rheumatoid arthritis.¹² Whereas there is no active inflammatory process or quiescence of the disease in osteoarthritis, any inflammation from mechanical insult should have subsided before operation is undertaken. More surgical procedures are performed for disability at the hip and knee than for any other joints.

Manipulation under anesthesia is performed in osteoarthritis for the joints of the cervical spine, the shoulder, the hip, the knee and the foot. It has been suggested that impingement and irritation of cervical nerves can be relieved at times by gentle manipulation of the cervical spine. Osteoarthritis of the shoulder is frequently associated with fascial and capsular irritation and subsequent adhesions. These can be released, and freer and less painful motion may result. Mennell⁷² has demonstrated that improved motion may follow manipulation of the hip in osteoarthritis if there is not much deformity of the femoral head. Sometimes, repeated gentle manipulations remove almost all disability. Manipulation is rarely required at the knee. If there is much limitation of extension it is usually the result of an internal derangement, and arthrotomy is often required.⁷³ A rigid valgus deformity of the foot is occasionally seen in osteoarthritis. Manipulation and fixation in a corrected position in a plaster cast, with later a support to the foot, often relieve this

Neurectomy

Cutting of the obturator nerve has been said to relieve most of the pain in osteoarthritis of the hip joint. The sensory distribution to the hip joint is extensive, but most of the anterior distribution comes from the obturator nerve.⁷³ This is cut within the pelvis just before the nerve enters the obturator foramen. Sometimes, for completeness, fibers coming to the posterior capsule with the nerves to the external rotators of the hip are also cut. This operation, which is not a serious surgical procedure, is usually reserved for elderly persons in whom relief of pain, rather than improvement in function, is the chief desideratum. Denervation has been reported in other joints, but here it has as yet not passed the experimental stage.

When there is much limitation of motion from osteoarthritis in early middle age, various plastic procedures have been described to remove the bony overgrowth and to improve motion. Cheilotomy gives relief until the re-formation of overgrowth again limits motion about the joint. Partial cheilotomy and acetabuloplasty⁷⁴ give temporary relief only. At the hip, arthroplasty⁷⁵ is useful in monoarticular disease (so-called secondary osteoarthritis in younger persons). At the knee a partial synovectomy and trimming of bony overgrowth have lessened pain and increased motion.^{62, 76}

Removal of the patella when it was markedly overgrown and interfered with function was advocated by Berkheiser.⁷⁷ Subsequent reports have been conflicting,⁷⁸ but most recent reports and my own experience suggest that the patella is essential for the normal mechanics of extension at the knee.⁷⁹ Plastic procedures on the patella seem to give a better functional result than complete removal.

Degeneration of intra-articular ligaments and other structures about the joint in osteoarthritis are commonly found. At the shoulder partial or complete tears of the supraspinatus tendon are a frequent accompaniment. In the lower back, ruptures of the intervertebral disk are a not uncommon complication of osteoarthritis. Unless there is severe sciatic pain the diagnosis may be difficult. Operative removal of the extruded disk substance is sometimes required both in the cervical and in the lumbar spine. At the knee in osteoarthritis, internal derangement is often evidence of a foreign body or a displaced meniscus. Relief of pain and surprising recovery of function often follow arthrotomy.

At various times attempts have been made to improve the circulation about the joint with the mistaken idea that in this way a halt could be made in the degenerative process and that a regression in the periarticular overgrowth might result. One of the earliest means employed was forage,⁸⁰ a drilling into the bone to provide new channels for vascularization. This has been carried out at the hip joint more often than any other joint. Here drill holes were

bored into the femoral neck. More recently, transplantation of available muscle, chiefly the vastus externus, has been made into the femoral neck to accomplish the same end.⁸¹

When there is much deformity from osteoarthritis at any joint a number of simple and helpful procedures have been reported to correct such a deformity.⁸² One of these is osteotomy. Although this procedure has been used on rare occasion at the acromioclavicular joint, the elbow joint and the wrist, it has been employed most extensively at the hip joint. The operation that has received the most attention has been the intertrochanteric osteotomy of McMurray.⁸³ This procedure is not particularly shocking. By it, adduction and external rotation of the leg can be fully corrected, and the femoral shaft can be displaced inward, changing the weight thrust a little and making for increased stability of the joint. Such procedures are usually reserved for patients in later middle life when correction of deformity is desired rather than increase in articular motion.⁸⁴

In the elderly patient many surgeons recommend complete stiffening of the painful joint for the relief of pain. One of the simple, earlier methods for obtaining this end was simple nailing of the hip through the neck into the acetabulum.⁸⁵ It was found that many hips with osteoarthritis failed to become ankylosed by this means. A number of more extensive procedures, some of them carried out in two stages, have been reported.⁸⁶

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Correction In the article entitled "Intensive Chrysotherapy (with Lauron) in Rheumatoid Arthritis" by Friedman and Steinbrocker, which appeared in the March 10 issue of the *Journal*, the value "microgm" in Table 4 on page 365 should be changed to "mg" throughout

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

CASE 35151

PRESENTATION OF CASE

A seventy-year-old farmer was admitted to the hospital because of a very productive cough

For several years he had a chronic cough, most severe in the morning, when he raised moderate amounts of whitish sputum. He was in otherwise good health for his age. Five months before admission the cough increased in frequency and productivity, so that at the time of admission he was raising about half a cupful of yellowish and occasionally blood-stained sputum each day. Progressive lack of appetite, weight loss and weakness appeared. A physician performed an x-ray examination eight days before entry. Penicillin therapy was given. The patient was told that he had a lung abscess that was increasing in size despite chemotherapy, and he was transferred here.

On admission he appeared weak and emaciated but in no acute distress. The tongue was red and smooth, he was edentulous, with an upper plate. The trachea was in the midline, and there were dullness to percussion and decreased breath sounds in the region of the right fourth rib posteriorly. There was no change in tactile fremitus. The heart was within normal limits. A small, indirect hernia was present in the right inguinal region. The prostate was twice the normal size but not hard. The blood pressure was 150 systolic, 90 diastolic.

The urine had a specific gravity of 1.026 and gave a + test for albumin. The white-cell count was 16,800, with 77 per cent neutrophils, 8 per cent lymphocytes, 8 per cent monocytes and 7 per cent eosinophils. The serum total protein was 6.06 gm per 100 cc, chloride 105 milliequiv per liter, and nonprotein nitrogen 24 mg per 100 cc. The prothrombin time was 23 seconds (control, 16 seconds).

An electrocardiogram on the fifth hospital day showed a normal rhythm at a rate of 75, with the PR interval equal to 0.15 second and normal axis. The T waves were low upright in Leads 1, 2 and 3, with upright T_{V₁}, V₄ and V₆ and flat T_{AVL} and low upright T_{AVR}.

X-ray examination of the chest showed an increased anteroposterior diameter. Both leaves of

the diaphragm were low, and fluoroscopically were seen to be limited in their excursion. The lung fields were bright. In the apex of the right lower lobe lying posteriorly in contact with the chest wall was a rounded shadow, 7 cm in diameter, in which there was a fluid level. The shadow was slightly lobulated in contour, and the upper portion of the wall of the cavity was seen to be irregular along its inner wall (Fig 1). There was little or no reaction in the surrounding lung. The sputum was negative for acid-fast organisms, and cytologic examination for tumor cells was reported as "doubtful." Bronchoscopy demonstrated no abnormalities except that the dorsal division of the lower lobe was somewhat reddened, and a thin, whitish, mucoid secretion exuded from it. There was no fixation or deformity here



FIGURE 1

or elsewhere. On the ninth hospital day a right lower lobectomy was performed. Toward the end of the operation the blood pressure fell to 90 to 100 systolic, 50 diastolic. At the end of the operation the blood pressure was up, and the condition was good. A blood transfusion of 2000 cc was given.

Twelve hours later the patient's general condition seemed good, although there was a hypotension (blood pressure of 80 systolic, 40 diastolic), without rise in pulse. Fourteen hours after operation the blood pressure dropped to 60 systolic, 40 diastolic, and a marked bradycardia (rate of 44) appeared. An electrocardiogram showed an irregular auricular and ventricular rhythm, with auriculoventricular dissociation and prolonged QRS time. Many artifacts obscured the tracing, but the T wave in Lead 1 appeared upright, with a low upright T wave in Lead 2, inverted T wave in Lead 3 and depressed

ST segments in Leads CF₂ and CF₄, with probably upright T waves in Leads CF₂ and CF₄. He died thirty-six hours after the operation

DIFFERENTIAL DIAGNOSIS

DR LOWREY F DAVENPORT This is the recurrent problem of differential diagnosis between infection and tumor. Did this man have a simple lung abscess? Did he have an abscess that developed secondarily to bronchial obstruction, or was this a primary tumor in the lung with beginning central necrosis to account for the symptoms? I should like to see the x-ray films

DR STANLEY M WYMAN The posteroanterior and lateral views show this well rounded, quite discrete shadow of increased density far posteriorly in the right chest and somewhat medially, and it seems to be close to the chest wall. There is a clearly defined fluid level within this round shadow. The wall of the shadow itself is thickened, and its inner contour is shaggy and irregular as the record states. This is a Bucky film taken for rib detail and shows the ribs and the spine in this area to appear within normal limits. The heart shadow is a little prominent in the region of the left ventricle, and the aorta is quite tortuous. The chest generally is emphysematous.

DR DAVENPORT We have to explain, then, a localized lung lesion in the dorsal portion of the right lower lobe. The differential diagnosis here is between infection and tumor. I believe, in a man of this age with this large an abscess cavity, who had a sputum negative for tubercle bacilli, that we can with reasonable certainty rule out the consideration of tuberculosis. The differential diagnosis lies between a simple lung abscess and an abscess that developed in a necrotic tumor mass. The localization of the abscess in the dorsal portion of the lower lobe is not uncommon for a simple lung abscess. However, we have nothing in the background of this patient to explain the appearance of lung abscess. Presumably his teeth had been removed many years previously, and there is nothing in the history as given to suggest any possible etiologic agent for a lung abscess. Lung abscesses as discrete as this usually show surrounding pneumonitis unless there has been intensive chemotherapy. Rarely in a lung abscess do we see such a sharply demarcated lesion as presented here. Most tumors arising in the bronchial tree in the periphery of the lung of a solitary nature, and of this size, are adenocarcinomas. In such a situation these tumors frequently outgrow their blood supply and show a central necrosis. A Papanicolaou stain on the material taken from the patient's sputum showed a doubtfully positive test. I assume that the material from this tumor was so necrotic that even though he was raising tumor cells, it might be difficult to recognize them under the microscope. The remain-

ing findings at bronchoscopy are of no significance in a tumor situated as far posteriorly as this tumor was. We are given the symptom of chronic cough for several years. Apparently, that was the type of morning cough that a man who has spent seventy years of his life in New England is reasonably entitled to. The cough that became alarming and troublesome had been present for only five months. Cough of five months' duration is not unusual with a tumor such as this is, with a central necrosis. I would think, then, that the lung picture was that of a bronchiogenic tumor, probably an adenocarcinoma, undergoing central necrosis.

I think that secondarily it would be of some interest to try to puzzle out why he died within thirty-six hours of operation. When a patient dies within thirty-six hours of a major operation such as a lobectomy we should like to know, first, whether or not a suture had slipped following cough as he began to rouse from the anesthesia. However, with the drop in blood pressure the pulse did not become elevated. This bradycardia excludes the possibility of blood loss as explanation for the low blood pressure and symptoms twelve hours after operation. Over and over again we get confused between the differential diagnosis of pulmonary embolism and coronary occlusion. Pulmonary embolism may give a definite pattern of symptomatology. In a certain percentage of cases there are suggestive changes in the electrocardiogram. No changes diagnostic of pulmonary embolism were present in the second electrocardiogram, but the tracings suggest coronary occlusion. The secondary shock in a man of seventy who has arteriosclerosis of the coronary arteries may cause acute coronary occlusion. Whatever the trigger mechanism that precipitated the cardiac episode, a man who develops a sharp drop in blood pressure without evidence of blood loss, a cardiac rate of 42 and complete dissociation by electrocardiogram of auricular and ventricular rhythm must have a profound disturbance of cardiac conduction mechanism, presumably on the basis of coronary occlusion.

My final diagnosis is primary carcinoma of the bronchus and death thirty-six hours following operation from an acute coronary occlusion.

DR DONALD S KING Can you distinguish between abscess and tumor by the thickness of the wall and the shaginess of the wall?

DR WYMAN No, not in all cases. I think, as Dr Davenport pointed out, that the thickness and contour of this wall together with the absence of the reaction about it, definitely favor tumor over an inflammatory process such as abscess. The two overlap, however, in certain cases and make it impossible to be certain.

DR ALFRED KRANES Knowing the tendency of these tumors to metastasize to the adrenal glands, could you consider acute adrenal insufficiency as a

possible mechanism for the hypotension following operation and the events that followed it?

DR DAVENPORT I do not think I would consider it as a probability I might consider some such mechanism in the development of the low blood pressure, in the absence of anything else to explain it We have no evidence of adrenal disorder prior to operation, and it seems hardly likely that he developed such a condition within thirty-six hours of operation

DR KRANES Except that this degree of surgery might be enough to throw a person into acute adrenal insufficiency He had no previous sign of it, and I do not think that one can make the diagnosis It is just speculation

DR EDWARD B BENEDICT I think it is worth pointing out why we did a bronchoscopy on a tumor that was obviously quite peripheral and beyond the reach of the bronchoscope We did it because sometimes we can find tumor cells in the bronchoscopic washings when we have negative cytologic findings in the sputum

DR BENJAMIN CASTLEMAN In this case a cytologic examination of the washings showed definite tumor cells Then Dr Soutter took over

DR LAMAR SOUTTER There is one interesting point about the lack of surrounding pneumonitis This patient had been on large doses of penicillin for a month prior to entry so that one could expect less pneumonitis than is usually found with an abscess It might be questioned why anyone would do lung surgery on a patient of seventy who had emphysema If he had had a benign abscess it could have been drained, which would have been a simpler procedure than a lobectomy But because we believed that he had a malignant lesion and was going steadily downhill, we thought it reasonable to do a lobectomy on this man to rid him of his sepsis This procedure for a peripheral tumor has a reasonable chance of effecting a cure and is much safer than a pneumonectomy in older patients We believed that he would withstand such a procedure but not a pneumonectomy He was seen by a cardiologist, who thought that the heart was all right The operation was long, and the dissection was difficult because of the inflammatory changes around the hilus of the lung Toward the end he had a sudden fall of blood pressure accompanied by bradycardia We discussed with the anesthetist at that time the possibility of adrenal insufficiency, which Dr Kranes mentioned We gave him neo-synephrine, to which he had a favorable response Postoperatively, when he again had a fall of blood pressure with bradycardia we thought of hemorrhage But he had only a moderate amount of bloody fluid coming from his chest drainage tube We gave him another transfusion, which did not affect his blood pressure His bradycardia persisted The cardiologist suggested that it was probably

on the basis of myocardial failure That is why an electrocardiogram was taken

DR RICHARD CLARK There were two tracings done before the final episode These are of value, primarily as showing nothing of great significance and as serving as a base line This is the one taken after the operation, and it does show more than is described in the protocol There is a distinct depression of the ST segment in Lead 1 of approximately 1 mm, a distinct elevation of the ST segment in Lead 2 of approximately 2 mm and distinct elevation of the ST segment take off in Lead 3, whereas in Leads CF₁ and CF₂ there is significant depression of the ST segments The T waves themselves are somewhat obscured by the superimposed P waves going with the auriculoventricular dissociation I think this tracing is entirely consistent with an acute posterior myocardial infarction, which also involves the conduction system

CLINICAL DIAGNOSES

Carcinoma of lung, right
Right lower lobectomy, recent
Coronary thrombosis
Myocardial infarction, recent

DR DAVENPORT'S DIAGNOSES

Bronchiogenic carcinoma
Acute coronary occlusion

ANATOMICAL DIAGNOSES

(Squamous-cell carcinoma of lung)
Operation lobectomy
Acute coronary thrombosis
Myocardial infarct, recent
Tuberculosis, old, bronchial lymph nodes

PATHOLOGICAL DISCUSSION

DR CASTLEMAN Dr Soutter removed the lower lobe with a portion of two ribs to which the tumor was adherent In the center of the lesion was a necrotic cavity surrounded by irregular and nodular, granular tumor Microscopically it was a squamous-cell carcinoma, Grade III The regional lymph nodes showed no metastases, but there was old tuberculosis The final affair, both as Dr Clark and Dr Davenport predicted, was an acute thrombosis of the right coronary artery This vessel supplies the interventricular septum and posterior wall, which was infarcted Microscopical examination of the infarct showed an extensive infiltration with leukocytes, such as one sees in an infarct about two days old It would be interesting to decide whether this infarction could possibly have occurred before the operation or just before or even during the induction of anesthesia I do not see how we can settle from the section of the myocardium whether it was thirty-six or forty-eight hours old Certainly, it was within

that range. The polymorphonuclear leukocytes were still well defined and had not begun to degenerate very much. The myocardial fibers themselves were granular and had lost their striations. We found no metastases anywhere in the body.

CASE 35152

PRESENTATION OF CASE

A seventeen-year-old grocery clerk was admitted to the hospital because of an abdominal mass.

The patient had been in excellent health until two months before admission, when he noted the onset of severe, gnawing pains coming on four to six hours after meals. These were confined to the left hypochondrium and relieved by food. Associated with this was regurgitation of food shortly after

episode of jaundice and clay-colored stools, both of which subsided spontaneously. The remaining past history was completely noncontributory.

Physical examination revealed a well developed young man, showing some pallor and evidence of weight loss. The cervical and axillary lymph nodes were just barely palpable. The heart and lungs were normal. There was a large, hard mass in the left hypochondrium, filling the left upper quadrant. It was slightly tender and moved with respirations. The liver edge was palpable two fingerbreadths below the right costal margin. The right testicle and epididymis were enlarged, measuring together 5 by 4 by 3 cm. There was no history of injury, and the mass was nontender. The patient stated that one month before admission he had noticed the right testicle becoming larger than the left.

The temperature was 99°F, the pulse 100, and the respirations 18. The blood pressure was 130 systolic, 88 diastolic.

The urine showed a ++ test for bile and an occasional white blood cell. The blood hemoglobin was 10 gm. The white-cell count was 8000, with 86 per cent neutrophils, 6 per cent lymphocytes, 4 per cent monocytes, 2 per cent basophils and 2 per cent immature cells. The serum nonprotein nitrogen was 26 mg., and the total protein 5.7 gm. per 100 cc., the chloride 97 milliequiv. per liter, and the prothrombin time 20 seconds (control, 15 seconds). The stool was guaiac negative.

On the fourth hospital day gastroscopy was attempted, but neither the operative gastroscope (Benedict) nor the smaller gastroscope (Schindler) passed through the cardioesophageal junction. The cardiac orifice was dilated slightly with a No. 20 Fr. bougie, but no tumor could be seen. A roentgenogram of the chest showed a fine, strand-like increase in density throughout both lung fields. There was no enlargement of the hilar lymph nodes. There was an incidental finding of an old, healed fracture of the right tenth rib posteriorly. A gastrointestinal series showed a normal esophagus. There was a large, lobulated, firm mass surrounding the stomach and apparently inside the greater wall, extending from the fundus to the pylorus. Normal mucosal folds could be seen only in the extreme portion of the fundus. There were some very thick folds along the greater-curvature side (Fig 1). A large, apparently intraluminal ulcer, 7 cm. in diameter, was present on the lesser curvature. There was no peristalsis, and the entire stomach was rigid, fixed and unpliant. There appeared to be enlargement of both liver and spleen. On the sixth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR J GORDON SCANNELL. I think it is of considerable interest that there was a low lymphocyte count. It may be of significance.



FIGURE 1

eating, which caused him to limit himself to a semi-liquid diet. Three weeks prior to entry a mass was found in the left hypochondrium, and at about this time he complained of the feeling of food seeming to "stick" in the region of the umbilicus. He also passed two bulky, tarry stools following which he became progressively more constipated. One week before admission the onset of low thoracic back pain, more marked at night, was noted. Despite these symptoms and a weight loss of 15 pounds, his appetite remained excellent, and he continued his usual activities, such as playing hockey in the evening. There was no malaise, hematemesis or known fever. Four years before admission he had a seven-day

Before looking at the x-ray films, which should be extremely helpful, we might review the history and see what definite leads we can get from the symptoms. Certainly, the patient had a good many symptoms involving the gastrointestinal tract. The pain, in a certain sense, could not have been more characteristic of ulcer, and he also had evidence of obstruction, although I would interpret the evidence of obstruction to be more indicative of motor disturbance of a large organ rather than obstruction distal to an organ that contracted. He did not have cramps, and he was without nausea, pain and real vomiting, although he had regurgitation of recently eaten food. He had some bleeding in the past presumably, and he certainly was anemic, which in a male patient connotes blood loss. It is interesting that he had a guaiac-negative stool in view of the fact that a large ulcer was visualized on x-ray study. He had lost weight, in spite of all this the appetite was good, which I think would be extremely unusual for a large, primary neoplasm of the stomach. The second lead, which occurs to me from the history is the evidence of retroperitoneal involvement by whatever process we are dealing with. He had low dorsal pain, worse at night, which sounds as if he had something in the retroperitoneal area high up. Secondly, there is some evidence of biliary-tract obstruction, indicated by the fact that he had some bile in the urine. We wonder a little later if he had splenic-vein obstruction, with the enlargement of the spleen. The third obvious feature is the painless, nontender, testicular tumor coming on without antecedent history of trauma and attaining significant size in a short time.

The physical signs are important. There was essential absence of peripheral lymph nodes, so that would tend to steer away from the diagnosis of lymphoma. He had a large, hard mass in the left upper quadrant. This mass moved with respirations, which, I suppose, means that it was intraperitoneal in nature, although it seems to me difficult, with a large mass that has not a great deal of inflammatory fixation, to say that is necessarily so because I think a retroperitoneal mass, if large and nodular enough and not much inflamed, could move with respirations merely from the diaphragm downward. I am impressed by the description of the testicular tumor, which was localized to the testis itself and possibly the epididymis, did not invade the adjacent structures, and did not extend up the cord.

DR JOHN M RAKER It is only fair to note that the other testicle had the same consistence and was also slightly enlarged.

DR SCANNELL I think I would rather have not known that I have to now. The testicular mass was firm but not stony hard?

DR RAKER It was quite hard.

DR SCANNELL The laboratory studies showed a lymphocytopenia, and I think that that might be indicative of low obstruction to the thoracic duct, which is one of the normal paths of the lymphocytes into the circulating blood. He had an anemia. We do not know the red-cell count, but probably do not need to. He had a ++ test for bile in the urine, unsupported by other evidence, I suppose that is indicative of some regurgitative type of jaundice. He might well have had a low-grade obstruction of the lower end of the biliary tract.

May we look at the x-ray films?

DR STANLEY M WYMAN The films of the chest show a possible minimal increase in the linear markings, but this is not very striking. I can see no localized disease in the lung fields, and the heart shadow is not remarkable. The old fracture of the right tenth rib is seen, and there is no evidence that this is pathologic. The strikingly abnormal stomach is well seen on this series of films, and the abnormality appears to extend from the extreme cardia to the immediate prepyloric region. The stomach maintains a constant contour, with very markedly thickened, irregular, possibly nodular, mucosal folds, with a tremendously large ulceration on the lesser-curvature side of the stomach, which appears to fall within the projected lumen of the stomach — at least in part. There is a suggestion, but nothing more definite, of a surrounding soft-tissue mass at several points in the stomach. The most important observation is the fluoroscopic observation that the stomach was rigid. The spleen can be faintly outlined, and it appears enlarged. The liver edge is less well visualized, and I am not so certain about the degree of possible hepatic enlargement.

DR SCANNELL Your opinion is, then, that there is an intrinsic lesion of the stomach as well as extrinsic.

DR WYMAN I can see no definite evidence of an extrinsic lesion of the stomach, and I would call this intrinsic disease in the stomach itself, a process that infiltrates the entire stomach wall from the cardia to the prepylorus.

DR SCANNELL Could it be something growing through the stomach from outside in?

DR WYMAN I do not believe so, since it involves all the organ and seems to involve it rather uniformly. With something extrinsic I would expect it to involve one portion or another primarily.

DR SCANNELL You do not believe that something arising in the peritoneal cavity on the peritoneal coat of the stomach and invading the wall could give secondary changes in the mucosa?

DR WYMAN I do not believe it could be so extensive and so uniform. I would expect it to be localized to one region or another, probably on the lesser curvature.

DR SCANNELL I am getting more and more into deep water the more help I get.

I want to go back to the testicular tumor. There is no evidence of lymphatic blockage and no evidence of lymphatic metastases. In arriving at a diagnosis it seems reasonable to assume that the patient had a malignant lesion, and I think if it were not for the testicular tumor lurking malevolently in the background, one could make a strong case for a primary lesion in the stomach. These are admittedly rare in this age group but not unheard of. If it were a malignant tumor of the stomach, it would be something along the line of the lymphoma group — lymphoblastoma or something of that nature. But we have no other evidence of lymphoma, and it is very striking that these gastric symptoms are what they are if the tumor is primary there. Therefore, at a considerable risk, I am going to admit that it might be that, but I am more impressed by the testicular swelling and I think that the testicular tumor could give rise to these symptoms as given. I suppose, before going down farther, we should mention the other organs of the left upper quadrant, — the spleen, pancreas, kidney and left adrenal gland, — but there is no specific evidence to incriminate any of these. However, testicular tumor, as I would visualize it, would have to give rise to extensive retroperitoneal metastases in the region of the root of the mesentery, in the cisterna chyli and thoracic duct, and also peritoneal metastases to account for the picture as given. Of the testicular tumors, this is not an unlikely performance for a seminoma. I am using for my authority a recent report by Friedman and Moore* of some 922 cases studied in the Army Insti-

tute of Pathology, which recorded the accumulated experience of the last war. Friedman and Moore believed they could fit testicular tumors into four groups in which seminoma was as common as any other. They tended to occur later in life. They usually were restricted in that they did not invade massively at the local site but did tend to invade the retroperitoneal area and the peritoneal lining, which seems to have occurred in this patient. Other testicular tumors, which they group as embryonal carcinomas and which include the chorionepitheliomas, tend to invade locally and metastasize to the lung or liver. This patient did not show this. He had no secondary endocrine changes such as these patients frequently show or at least have demonstrated by urinary assay. A third type, which the authors report, are teratomas. These may be either adult, in which case they are considered relatively benign, or teratocarcinoma. Teratocarcinoma merely means a teratoid tumor in which definite malignant cells can be identified. These usually metastasize by virtue of their obviously malignant elements. They also metastasize to the parenchymal organs. The adult teratoma, which is usually benign, may metastasize as a relatively adult tumor, although this is comparatively rare.

I assume that, since Dr Wyman has said that this probably was an intrinsic stomach lesion, I am displaying rank ingratitude to ignore it, but I think we can explain the picture on a seminoma, which developed massive retroperitoneal metastases in the region of the celiac axis and involved the stomach in the region of the cardia, where the stomach is really a retroperitoneal organ. The tight constriction, as it were, about the stomach would produce the secondary changes in the luminal portion.

DR ALFRED KRANES I do not quite understand why Dr Scannell ruled out lymphoma.

DR SCANNELL I believe that we cannot rule it out. We have no other lymph nodes involved, but we do have a testicular tumor that could account for the symptoms.

DR KRANES The enlargement of the spleen?

DR SCANNELL The enlargement of the spleen could have been on the basis of obstruction of the splenic vein or retroperitoneal metastases.

DR EDWARD B. BENEDECT I would bet on a primary tumor of the stomach, partly on the basis of what Dr Wyman describes and partly because when the gastroscope meets complete obstruction at

*Friedman, N. B., and Moore, R. A. Tumors of testis: report on 922 cases. *Mil Surgeon* 99:575-593, 1946.

the cardiac orifice, it usually means primary tumor of the stomach

DR RAKER The other testicle with the same consistence does not disturb you, Dr Scannell?

DR SCANNELL It disturbs me, yes

DR WYMAN Roentgenologically, this picture is most consistent with lymphoma of the stomach

DR MILFORD D SCHULZ To confuse the picture a little more, I looked at some films from this patient about an hour ago, and the stomach looks today not unlike what it did at the first examination here, after having been subjected to a period of two weeks of x-ray treatment. The patient received something like 1250 r in the region of the stomach, and there had been no demonstrable change

DR BENJAMIN CASTLEMAN This patient was operated on by a team of urologists and surgeons. Perhaps they can answer some of the questions

DR WALTER S KERR When I saw him the right testicle was twice the normal size, the left testicle was normal. Two days later the right one had grown twice the size and the left one three times the original size — a matter of a few days. We explored the right testicle and found that it was involved by a uniformly appearing tumor. Dr Moorman took over at that stage

DR HENRY D MOORMAN I explored the upper abdomen and took a biopsy from the involved wall of the stomach. The peritoneal cavity contained a large quantity of fluid, quite cloudy in appearance. The tumor seemed to arise intrinsically in the stomach in the sense that the tumor did not break out through the anterior serosal surface. We merely biopsied the anterior surface of the stomach because the whole mass was thick, and apparently all the retroperitoneal lymph nodes were involved

CLINICAL DIAGNOSES

Gastric neoplasm, ? lymphoma
Tumor of testis

DR SCANNELL'S DIAGNOSIS

Seminoma of testis, with retroperitoneal metastases and extension into stomach

ANATOMICAL DIAGNOSIS

Malignant lymphoma, reticulum-cell-sarcoma type, of testis, stomach and retroperitoneal lymph nodes

PATHOLOGICAL DISCUSSION

DR CASTLEMAN We received a small biopsy from the stomach and the entire right testis. Grossly the testis had almost the same consistence of a normal testis, but on section the surface appeared to be uniformly replaced by a soft, pinkish-gray, obviously neoplastic tissue. Microscopically, however, the tubules of the testis persisted, and the tumor cells infiltrated between them without destroying them. In other words, the entire organ was not replaced by the tumor, but the tumor was interspersed between tubules, a finding very much against a primary tumor of the testis and more in keeping with a lymphoma, which is what this lesion was. It was a very rapidly growing lymphoma of the reticulum-cell-sarcoma type, and the biopsy from the stomach showed a similar appearance. We believe that lymphomas arise independently in various parts of the body rather than metastasize from one place to another. One can argue that this was primary in the stomach and metastasized to the testis, but it is more likely that it arose independently in the stomach, retroperitoneal lymph nodes and testis and apparently now in both testes.

A PHYSICIAN Are reticulum-cell sarcomas resistant to x-ray therapy?

DR SCHULZ Ordinarily, no. Perhaps the reason why the lesion has not changed is that a sufficient amount of time has not elapsed.

DR CASTLEMAN Are you using the 200 K V or the million-volt machine?

DR SCHULZ The million-volt machine — it does not matter which one uses as long as it gets to the tumor. Of course, a larger dose can be given with the million-volt machine with less skin damage.

DR DONALD S KING How often do you see a lymphoma of the testicle?

DR CASTLEMAN We have seen 2 cases, I believe, in which lymphoma was limited to the testicle, and I believe we have seen several cases with extensive disease throughout the body in which the testes were also involved.

DR KING It is uncommon, I should say.

DR CASTLEMAN Yes. I believe that when lymphoma does occur in the testis, it is usually this type of lymphoma. I wonder if the immature cells seen in the peripheral blood were monocytes, which would fit in with this type of disease.

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In that same essay the Baltimore physician commented on the records he had kept of some five hundred deathbeds, describing the apparent sensations of the dying although a small number suffered bodily pain or distress, very few indeed showed mental apprehension or terror. "The great majority gave no sign one way or the other, like their birth, their death was a sleep and a forgetting."

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Streptomycin-resistant and streptomycin-dependent variants have also been obtained by Paine and Finland^{3,4} from sensitive strains of a variety of different pathogenic organisms, including *Staphylococcus aureus*, *Escherichia coli*, *Proteus morganii*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, and Yegian and Budd⁵ obtained similar variants from a strain of *Mycobacterium ranae*, which is not a pathogenic organism. The former authors found that their truly resistant variants retained this characteristic on repeated subculture, either in the presence of streptomycin or in its absence, whereas prolonged incubation of the dependent organisms

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The finding of streptomycin-dependent variants, apparently developing during treatment with streptomycin, has now been reported by two separate groups of observers.^{6,7} Spendlove et al.⁶

isolated a streptomycin-dependent strain of *Mycobacterium tuberculosis* on the ninety-sixth day of streptomycin treatment. This was discovered during routine streptomycin sensitivity testing of the strains when it was noted that growth was poor in the control tube without streptomycin while it was abundant in all tubes containing streptomycin in concentrations ranging from 1 to 1000 microgm per cubic centimeter. This patient's infection showed rapid progression during the course of streptomycin therapy, and no striking change occurred after this treatment was stopped.

In this case, a strain of tubercle bacillus isolated three months later had similar characteristics, it failed to grow in mediums without streptomycin and grew in the same mediums when concentrations of streptomycin from 1 to 1000 microgm per cubic centimeter were added. If the findings as reported are correct they suggest either that the patient was supplying some factor that served in place of the streptomycin in supporting the multiplication of the dependent variants or that some of these variants arose during the course of the streptomycin treatment and persisted without multiplying in the patient after the antibiotic was discontinued.

More recently, Miller⁷ looked for streptomycin-resistant or streptomycin-dependent organisms in animals and in patients under treatment with streptomycin. He gave normal rabbits and mice large doses of streptomycin and made periodic cultures of the pharynx and large bowel on mediums containing 400 microgm of streptomycin per cubic centimeter. After a week both Type A and Type B variants were recovered in these animals. He made similar pharyngeal cultures on patients who were being treated with streptomycin and obtained positive cultures in 98 per cent of these patients by the thirteenth day of treatment. In addition, about 10 per cent of patients not receiving streptomycin and 4 per cent of the staff, students and laboratory personnel yielded a few organisms in similar cultures. The highest incidence of positive cultures among controls — 21 per cent — was obtained from the nurses and maids working on the wards. All the strongly positive cultures were from the nurses who were caring for patients receiving streptomycin. The organisms recovered from these cul-

tures were predominantly the truly resistant or Type A variants, but a certain proportion were streptomycin-dependent or Type B.

These findings suggest that streptomycin-resistant organisms that developed in the throats of the treated patients were transferred to the nurses who looked after them. Although most of the organisms obtained in this study were presumed to be nonpathogenic, the possibility of transmitting resistant strains that are pathogenic is clearly evident.

Hobby and Dougherty⁸ have described still another type of streptomycin-resistant variant capable of multiplying in an aqueous solution of streptomycin that contains no other added nutrients.

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MEDICAL DEFENSE BOTTLENECK

Doctor shortage in the armed forces is no longer news, but its importance is increasing so rapidly that the Secretary of Defense recently called a press conference to issue an urgent warning. He gave facts, stated alternatives and disclosed plans.

Owing chiefly to the expiration of ASTP and V-12 tours of duty, the armed forces, already numbering almost 1,700,000, will lack 2760 medical and dental officers by July and by December will lack 3600 "Normal procurement channels" — that is, the present volunteer system — offer the only means of making good this shortage, and January's record of 30 new Medical Corps and 20 new Dental Corps commissions may be taken as a fair sample of its inadequacy. "We are in grave trouble and it is getting worse" according to a memorandum to the Secretary of Defense from the Air Secretary, and "In the Army the situation is

more serious than in the Air Force' adds the Under Secretary of the Army. Failure to mention the Navy does not imply that the Navy is any more fortunate. Medical manpower is the bottleneck of the armed-forces expansion program, and a real solution must be found.

Four alternatives appear, of which only the fourth is presently favored by the Department of Defense. One is to ask for a draft of physicians and dentists in the numbers needed, the second is to request reserve officers who served in World War II to return to active duty, the third is to require the men now on active duty to remain after their time of service is up, and the fourth is to appeal to the 15,000 men who have not served, all of whom were deferred during the war and some of whom (8000) received part or all of their professional training at Government expense. The Secretary of Defense made the following statement:

I believe these 15,000 men who saw no service overseas and who were not exposed to the rigors of war will themselves recognize our right to appeal to them to make a contribution in this emergency. In a democracy, this procedure is fair, equitable, and just. As Americans, I am confident that they will recognize their obligations if they are acquainted with the facts.

The Secretary is taking steps to implement these beliefs. By personal letter he will invite those trained at Government expense to accept commissions through local professional leaders; he will appeal to those who were deferred from the draft, and excused from combat to complete their professional education at their own expense, to apply for commissions, and by a publicity campaign he will enlist nation-wide support and understanding of the Defense Department's position.

An essential part of this program has been assigned to the Armed Forces Medical Advisory Committee composed of the surgeons general of the Army and Navy, the Air Surgeon and eleven distinguished civilian doctors under the chairmanship of Mr. Charles P. Cooper. Their task is to restore public confidence by eliminating professional manpower waste in the armed forces, thus removing the most serious stumbling block to volunteer service. It can be accomplished by merging the strength of the three services by defining and streamlining their workload, by raising professional standards

and by ensuring that "in so far as possible, each volunteer serves in an assignment commensurate with his professional skill and ability" so that his one or two years of military service will not be time lost. Should this immense undertaking succeed — and there is reason to believe that it will — a further debt of gratitude will be owed to the committee members, who, both in the regular components and as volunteers, have already rendered distinguished services to their country during the war.

Should this enlightened volunteer system fall short of meeting the manpower crisis, there will be no alternative but the draft, and whatever one may think of its fairness and its efficiency there will be no further possible doubt of its necessity. "For want of a nail the shoe was lost, for want of a shoe the horse was lost, for want of a horse the rider was lost" is the way *Poor Richard's Almanac* put it almost two hundred years ago. The modern version might read: for want of medical officers the armed forces were lost, for want of armed forces the peace was lost, and for want of the peace western civilization was lost. Whatever the price of success, one way or another it must be achieved now, for the price of another failure is too great for humanity to contemplate.

STUDY OF MATERNAL DEATHS

THE attention of fellows of the Massachusetts Medical Society and other readers of the *Journal* who reside and practice in Massachusetts is directed to the letter from Dr. Gillespie published elsewhere in this issue.

A five-year program has been initiated by the Committee on Maternal Welfare of the Massachusetts Medical Society, in conjunction with the Division of Maternal and Child Health of the Massachusetts Department of Public Health, for the study of all maternal deaths in the Commonwealth, whether they occur at home or in the hospital. All deaths within three months of the termination of pregnancy are to be included.

The purposes of the study are to determine exactly the total number of such deaths each year in the Commonwealth and the percentages at some

and in the hospital, to determine as exactly as possible the causes of all such deaths and their preventability, and to publish each year the number and causes, the findings of the study and the recommendations of the committee, both general and specific, for the improvement of maternal care

So far as available statistics are concerned it is known that there were approximately 125 maternal deaths in the hospitals of the Commonwealth in 1948. It is not known with any exactness how many of the deaths at home took place before or after delivery and might be accountable to the pregnancy, nor is it known how many mothers died of contributory causes that might not be obstetrically listed. Thus, in the autopsy of sudden deaths suggestive of pulmonary embolism and thrombosis, the attention of physicians and pathologists is called to the possibility of amniotic-fluid emboli and the methods employed to prove such a diagnosis.*

The committee, in order that these important data may be obtained, strongly urges all physicians to report promptly to either physician mentioned in the communication all maternal deaths, wherever they may occur.

*Gross P and Benz E J. Pulmonary embolism by amniotic fluid. *Surg Gynec & Obst* 85 315-320 1947

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

CHISHOLM — Miles D Chisholm, M D, of Westfield, died on December 19. He was in his seventy-second year.

Dr Chisholm received his degree from University College of Medicine, Richmond, Virginia, in 1900. He was formerly city physician in Westfield and was a member of the staff of the Noble Hospital. He was a fellow of the American College of Surgeons and the American Medical Association.

His widow, a daughter and two grandchildren survive.

CROSS — Albert E Cross, M D, of Worcester, died on November 6. He was in his seventy-seventh year.

Dr Cross received his degree from Boston University School of Medicine in 1900. He was a member of the board of governors of the Hahnemann Hospital and was a member of the American Academy of Ophthalmology and Otolaryngology and the New England Ophthalmological Society and a fellow of the American Medical Association.

His widow and two daughters survive.

HEALY — James C Healy, M D, of Boston, died on November 19. He was in his forty-seventh year.

Dr Healy received his degree from Tufts College Medical School in 1927. He was assistant professor of pharmacology at Tufts College Medical School.

His widow, a son and a daughter survive.

McKENZIE — John R McKenzie, M D, formerly of Cambridge, died on March 16. He was in his eighty-second year.

Dr McKenzie received his degree from Harvard Medical School in 1894. He was formerly a member of the staffs of

Holy Ghost Hospital for Incurables, Cambridge, and Worcester City, Boston City and Boston Lying-in hospitals. He was a fellow of the American Medical Association.

His widow and two sisters survive.

McQUADE — Lewis S McQuade, M D, of Quincy, died on March 10. He was in his sixty-seventh year.

Dr McQuade received his degree from Tufts College Medical School in 1907.

A sister survives.

NEWELL — Franklin S Newell, M D, of Boston, died on March 3. He was in his seventy-eighth year.

Dr Newell received his degree from Harvard Medical School in 1896. He was professor of clinical obstetrics emeritus, Harvard Medical School and Massachusetts General Hospital, a member of the American Gynecological Society and a fellow of the American Medical Association.

A sister survives.

PATTERSON — William F Patterson, M D, of Medford, died on February 23. He was in his eighty-third year.

Dr Patterson received his degree from Tufts College Medical School in 1895. He was a fellow of the American Medical Association.

PEASE — Lewis W Pease, M D, of Weymouth, died on March 17. He was in his seventy-fourth year.

Dr Pease received his degree from Tufts College Medical School in 1902.

His widow survives.

SEWALL — Edgar F Sewall, M D, of Somerville, died on March 22. He was in his sixty-fourth year.

Dr Sewall received his degree from Tufts College Medical School in 1913. He was a fellow of the American Medical Association.

His widow, a son, a daughter, six grandchildren and a brother survive.

BOSTON MEDICAL LIBRARY

PORTRAIT OF SAMUEL DANFORTH

The portrait of Dr Samuel Danforth (Harvard College, 1758), Paul Revere's physician, by Gilbert Stuart, owned by the Boston Medical Library, has been placed on exhibit in the Colonial Gallery of the Museum of Fine Arts through the courtesy of Mr G H Edgell, director of the Museum. The portrait is on a temporary loan to the Museum. It is considered one of the better examples of the work of Gilbert Stuart.

MISCELLANY

MEDICAL DIRECTOR OF RED CROSS NATIONAL BLOOD PROGRAM

Dr Louis K Diamond, of Boston, has been appointed full-time medical director of the Red Cross National Blood Program. While discharging his new duties he will be on temporary leave of absence from the Children's Medical Center and the Harvard Medical School.

WATER POLLUTION CONTROL BOARD

Water-pollution control, for which an Act was passed by the Eightyeth Congress, is gradually reaching the stage where definite action may be anticipated. The six non-Government members of the Water Pollution Control Advisory Board

have recently been appointed by the President, and in March the five Government members were selected by Federal Security Administrator Oscar R Ewing

The Board will assist in planning a program to support and promote technical research in water-pollution problems, "to provide federal technical services to State and inter-State agencies and to industries and to provide financial aid in the formulation and execution of projects for abatement of stream pollution"

CORRESPONDENCE

STUDY OF MATERNAL MORTALITY

To the Editor Will you be so kind as to publish the following letter in a forthcoming issue of the *Journal*?

To the Hospital Administrator

The Committee on Maternal Welfare of the Massachusetts Medical Society under the chairmanship of Dr Duncan E Reid, obstetrician-in-chief of the Boston Lying-in Hospital and professor of obstetrics at the Harvard Medical School together with the Division of Maternal and Child Health of the Massachusetts Department of Public Health, is initiating a five-year program for the study of all maternal deaths in Massachusetts as of January 1, 1949

The Department of Public Health is financing this project through funds made available by the Children's Bureau and is vitally interested in obtaining the wholehearted support of this program from hospital administrators, all staff members of hospitals, and all practicing physicians in the Commonwealth

For Worcester and all hospitals west of Worcester, the obstetrician in charge of this program will be Dr Arthur F G Edgelow, 76 Maple Street, Springfield His telephone number is Springfield 4-5926 For the eastern part of the state, which includes all cities and towns east of Worcester, Dr Luke Gillespie, 1180 Beacon Street, Brookline, telephone Longwood 6-7773, will be in charge of the program

Doctors Edgelow and Gillespie will assign an obstetrician to investigate promptly all maternal deaths which occur in the hospital or at home during pregnancy, delivery, or postpartum. These maternal deaths should be reported by telephone to either Doctor Edgelow or Doctor Gillespie immediately and should include the name and address of the patient, date of delivery, date of death, place of death, and the name, address, and telephone number of the physician who cared for the patient.

It is suggested that any physician who is in doubt as to the procedure should contact either Dr Edgelow or Dr Gillespie.

We would appreciate it very much if this letter could be read at your next regular staff meeting and then posted on your bulletin board Enclosed duplicate is for your personal files

Should there have been a maternal death in your institution since January 1 which has not been reported, would you please report it to either of the two obstetricians named above

By direction of the Commissioner,
RICHARD P MACKNIGHT, M D, *Director*
Division of Hospitals

Commonwealth of Massachusetts
Division of Hospitals

LUKE GILLESPIE, M D

1180 Beacon Street
Brookline 46, Massachusetts

REGARDING MORAL PROBLEMS

To the Editor I agree with Dean Sperry in his article in the *Journal* of December 23 when he says that life is sacred

Why, may I ask, is life sacred? The answer must be that it is created by God—otherwise our premise does not hold There, I think, we have the answer to the problems of both birth control and euthanasia

Who are we to say when God shall give His gift or when He shall take it away? We boast of our scientific advances,

which have resulted in a tremendous decline in maternal morbidity and mortality and also in a greatly increased life expectancy, and yet we find groups of physicians and clergymen advocating both birth control and euthanasia To me it is not logical.

I believe that in matters of morals and ethics we should see things as black and white and not in shades of gray In such matters we ought to be guided by the Ten Commandments rather than by the passing custom of the day

MARGARET C McMANAMY, M D

Orange Massachusetts

LOWER-NEPHRON NEPHROSIS VS EXTRARENAL AZOTEMIA

To the Editor Dr James H Townsend, in his reply to the letter of Walter Hollander, Jr, in the February 10 issue of the *Journal*, states that the distinction between extrarenal azotemia and lower-nephron nephrosis is largely an academic one "We chose to call the disease extrarenal azotemia If Mr Hollander chooses to call it lower-nephron nephrosis, I should not object."

It appears to me that there are clinical and pathological differences between the two conditions

Clinically, edema is an infrequent finding in extrarenal azotemia In a review entitled "So-Called Extrarenal Uremia. A study of twenty cases," in the *American Journal of Medicine* (5:574-585, 1948), Murphy et al, eliminating cases in which vomiting was one of the major complaints, disclosed that in spite of more than an adequate fluid intake, orally and parenterally, edema occurred in only 2 cases One patient had a + ankle edema due to heart disease, and the other had portal cirrhosis as demonstrated at autopsy In lower-nephron nephrosis, edema generally develops, its severity depending upon the extent to which fluids had been pushed, as pointed out by Strauss in his study "Acute Renal Insufficiency due to Lower-Nephron Nephrosis," which appeared in the *New England Journal of Medicine* (239:693-700, 1948) In extrarenal azotemia low blood pressure is practically always found In Murphy's series only 1 patient had hypertension, and at autopsy he was found to have a chromophobe adenoma of the pituitary body In lower-nephron nephrosis, after renal shutdown, the blood pressure rises, according to Strauss

Any serious illness or injury may be the cause of extrarenal azotemia In its pathogenesis the common denominator appears to be diminished blood flow through the kidneys Lower-nephron nephrosis is produced by a wide variety of traumatizing conditions that have in common the main feature of shock

Pathologically, in lower-nephron nephrosis, the lesions occur in a similar region in all the cases, with selective tubular damage to the ascending loop of Henle and the distal convoluted tubules The glomeruli and the proximal tubules are only indirectly affected, as demonstrated by Hall and Luetscher in their review entitled "Renal Disease" in the *New England Journal of Medicine* (239:621-631, 1948) In a study of "Extrarenal Azotemia and Tubular Disease," which appeared in the *Journal of the American Medical Association* (134:441-446, 1947), Bell and Knutson found mild to severe hydropic degeneration of the proximal convoluted tubules in 20 of 84 cases They suggested that the tubular injury was in part or entirely responsible for the uremia In the remaining 64 cases there were no structural changes

In the case cited by Appel and Townsend in their article "Extrarenal Azotemia Report of a severe case with recovery," in the *New England Journal of Medicine* (240:95-97, 1949), the patient was not in shock He did not develop edema after the severe oliguria had begun, and the degree of hypertension (blood pressure of 144 systolic, 90 diastolic) was slight

Like Drs Appel and Townsend I choose to call the case one of extrarenal azotemia However, I believe that the difference between lower-nephron nephrosis and extrarenal azotemia is more than an academic one

JOSEPH G WEINER, M D
Philadelphia, Pennsylvania

BRITISH VIEWPOINT ON BRITISH MEDICINE

To the Editor If I have been somewhat tardy in writing this letter, it is because I am naturally hesitant to enter what is exclusively an American field. Medicine, however, knows no national boundaries, and I therefore feel constrained to present to my American colleagues my own interpretation of the situation in Britain, so vividly depicted by Dr Sweet in his article in the February 3 issue of the *Journal*. Although I can quarrel with only a few of his facts, I find it difficult to believe that these have been viewed with the objectivity called for in Dr Sweet's article.

Dr Sweet considers the British National Health Service from the points of view of the specialist and the general practitioner, but he completely ignores that of the patient, who, I should have thought, would also have been interested. From all reports reaching me, the lay public in general is liking the Health Service very much indeed, and this is obviously a very important fact.

Great play is made by Dr Sweet about the amount of form filling that a doctor has to carry out. There is a large amount, and nobody objects more than the doctor, but little of the increase is due to the Health Service, the main bulk arising from the shortages resulting from the war and from our subsequent dire economic situation. There is very little in the way of a black market in Britain, and the public at large prefers that necessities in short supply should be obtained by those most in need, rather than by those who can pay inflated or illegal prices. There are black sheep in every walk of life, and doubtless some doctors issue certificates on rather flimsy grounds, but it is a measure of the high esteem in which the medical profession is held by the public that doctors are asked to undertake so important if so irksome a duty.

I cannot agree that the doctor under the National Health Service is regarded by the patient, veteran or other, as being in some sort of sinister plot against him, in general, he is regarded as being impartial and fair-minded. As for the idea, advocated by Dr Sweet, of a patient touting doctors until he finds one whose opinion can be bought, I can imagine nothing more damaging to the integrity and good name of the profession, Judas had his price.

A great deal of space is devoted by Dr Sweet to describing the delay in providing a new building for a certain professional department. These facts are only too true, — all such building in Britain is difficult to obtain, — but it is also true that a certain number of dwelling houses and other buildings were destroyed by bombs. Nothing undermines domestic morale more than sharing a house with another family, and I think it is reasonable that the highest priority should be given to domestic building.

Dr Sweet also speculates about the amount of malingering that will be encouraged by a state health service. In fact all reports reaching me state that malingering is not a major factor. Almost all the new patients should have been seen long before, and most are very considerate and even rather embarrassed at either having to visit the doctor or having him to visit them — they know only too well how busy he is. Dr Sweet's implication that doctors should only see those who think that their complaint might be trivial, provided such patients can pay suitable fees, falls right outside my conception of medical ethics, what is more important, it falls outside that of a large number of laymen and politicians. A properly trained doctor, however busy, is obviously better able to judge whether or not a complaint is trivial than a layman who is influenced by the size of his bankroll.

It is unquestionably true that panel practice in Britain is often very dreary, and a busy practitioner has to transfer to specialists many cases that in this country he might first attempt to deal with himself. A better system should undoubtedly be developed if it were possible, but against the discomfort of the overburdened general practitioner, one must weigh the advantage to the average patient of at least having an expert to decide whether he is seriously ill or not. Perhaps we are attempting to give the public a better service than the facilities and number of doctors permit, this is a matter on which the profession in this country might well ponder.

Please do not think that I necessarily endorse in full the National Health Service in Britain. There will obviously be very many teething troubles, but we shall ultimately make it work, though many heads may fall in the process, and

though many aspects may have to be changed. I merely plead that these things be viewed as objectively as possible in their true context, since it is only by this means that you in America can derive benefit rather than harm from our experiment in Britain.

G. A. SMART

Massachusetts General Hospital, Boston

Dr Smart's letter has been referred to Dr William H. Sweet, who offers the following reply.

To the Editor I am chagrined to learn that Dr Smart interprets my statements to mean that patients should be encouraged to search out a doctor whose opinions can be bought or to consult one for trivial complaints if they can pay a fee. This is remote from the idea intended.

Dr Smart's observation that the British people like their new health service is hardly astounding when one considers that it purports to relieve them of all responsibility in connection with illness and that only a tiny fraction of the expense of this service is borne by the direct health-insurance contributions of the person himself. The tentative conclusion to which I came however was that the doctor's colossal load under these conditions precluded efficient action by him — nor does Dr Smart appear to challenge this.

He does condone grievous delays in vitally needed hospital construction even though patients on long waiting lists for admission to hospitals die in their homes before a hospital bed is available. He states "that the highest priority should be given to domestic building," because "nothing undermines domestic morale more than sharing a house with another family." For some time we in my family have been sharing our house with another couple and their children. Dr Smart will perhaps be relieved to learn that the morale of the entire *ménage* remains excellent, and if this arrangement has by any chance hastened the completion of the new buildings of the Massachusetts General Hospital and the New England Center Hospital we are that much happier.

WILLIAM H. SWEET

Boston

REGARDING THE FARREN HOSPITAL EPISODE

To the Editor With the summary administrative dismissal of 4 members of the Franklin District Medical Society from the medical staff of the Farren Memorial Hospital in Montague City, Massachusetts, in the three days before the election in November, 1948, a total of 20 doctors have lost their hospital privileges in western Massachusetts for publicly approving the "Birth Control" referendum on the Massachusetts ballot. The others were 12 in the Pittsfield area in 1942, and 4 in the Springfield area in 1946.

The first amendment to the constitution of the United States seems to guarantee the right of free speech without penalty, the citizens of Massachusetts in the same election overwhelmingly voted reapproval of this guarantee, the Massachusetts Supreme Court had certified this referendum to the ballot for public discussion and vote, and no promise, either written or oral, had ever been requested of any of these doctors before in connection with this amendment. The medical-staff by-laws have no such requirements. No hearing, either before or after dismissal, has ever been granted. No doctor has ever been reinstated except by signing a new application blank, which included a promise not to exercise this right of free speech, 4 doctors in the Pittsfield area have made this promise.

As president of the Franklin District Medical Society I held several consultations with the Sister Superior, and with 2 members of the Executive Committee of the Trustees, the two committees of the Society held meetings during the month of November, one of them with the hospital authorities. An energetic petition supporting reinstatement was voted by the Society and presented to the Board of Trustees. In spite of this abridgment of civil rights the petition was not even placed on the agenda for the meeting by the President. A petition by me as a twenty-year member of the Farren Memorial Hospital medical staff and simultaneously president of the District Medical Society was sent to the Most Reverend A. G. Cicognani, the Apostolic Delegate in Washington, and its receipt has been doubly verified. With the passage of several weeks, even with a follow-up letter, no answer has been received.

The situation in this district is different from that in others, in that alternate hospital facilities are limited. There is only one other hospital. Total county bed capacity is below requirements, and will remain so for several years. In addition, the Farren Memorial Hospital was built in 1900 by a private citizen, Bernard N. Farren, it was given to a Massachusetts tax-free public charitable corporation, he was so determined that it should only be used as a hospital that he had this legal restriction filed in the Registry of Deeds, he repeated this and added a further legal limitation in 1910, the Board of Trustees consisted, and still does as a continuing policy, of both Catholic and Protestant members, the Sisters of Providence act as the supervising agents, the hospital has always admitted patients of any race, creed and color, the hospital has been supported in part by all races, creeds and colors as a result of campaign for funds by the hospital, and doctors have always been selected on the basis of professional qualifications and abilities.

The dismissed doctors and a majority of the Franklin District Medical Society believe that admission to and dismissal from the staff of this hospital should still be based exclusively on professional qualifications and abilities. A large element of the community, who have supported the hospital without favoritism and whose hospital care has been jeopardized because of this further restriction of hospital medical care, support this stand. It is believed therefore that this report to the medical fraternity in Massachusetts should be made.

LAWRENCE R. DANE, M.D.

Greenfield, Massachusetts

SMOKE GETS IN ONE'S EYES

To the Editor Since the medical profession as a group seems to be on trial because of its reactionary conservatism and its adherence to the *status quo*, perhaps one more item of criticism is in order.

One wonders if the editor, because of the remunerative advertising by the cigarette interests and because perhaps the medical profession are as a group the greatest consumers of cigarettes, would venture to publish the enclosed clipping by a recognized authority, in the interests of cancer control.

Excessive smokers are four times as liable as nonsmokers to have cancer of the mouth and respiratory system, and even mild smokers are twice as vulnerable to the disease as persons who do not smoke, according to Dr. Herbert L. Lombard, director of the Cancer and Chronic Disease Division, Department of Public Health. — *Needham Chronicle*, March 16, 1949

J. WALTER SCHIRMER, M.D.

Needham, Massachusetts

Note The editor is required to take far bolder steps than this — Ed

DEPRIVATION OF LICENSE

To the Editor At the meeting of the Board of Registration in Medicine held March 24, it was voted to revoke the registration of Dr. Louis R. Medverd, 1210 Cambridge Street, Cambridge.

GEORGE L. SCHADT, M.D., Secretary
Board of Registration in Medicine

State House
Boston

AN OPEN LETTER

To the Editor A most critical professional manpower shortage is facing the medical departments of the armed forces. The urgency of the need for physicians and dentists can be judged from the fact that by July of this year the armed forces will have lost almost a third of their present staff of physicians and dentists. The tours of duty of these professional men will expire, and normal procurement measures cannot fill the vast number of vacancies that will arise.

By the end of July we shall be short about 1600 physicians and 1160 dentists. By next December this shortage will grow to 2200 physicians and 1400 dentists. This means that the armed forces will not have enough professional men to give minimum medical service to almost 1,700,000 men and women who are serving their country.

You and your publication have been asked many times for assistance in special drives and campaigns for the welfare of our country. You have at all times shown whole-hearted co-operation.

We have sought and received support in this campaign from the professional societies from the national to the community level. Deans of medical and dental schools and the heads of hospitals have also been asked to co-operate in this emergency.

The success of this procurement campaign will depend primarily upon public understanding and public support. The people of the United States must be made aware of the seriousness of the problem that faces us. If this shortage is allowed to develop, it could jeopardize our entire national defense program.

The medical departments of the armed forces and the Government ask your co-operation in averting a situation that could have serious effects on the security of this country. Through your editorial pages and news columns you can help us inform the people of this country of the vital needs of the medical departments of the armed forces. You can urge young men who received their medical and dental educations during the war years, and who have given no service, to volunteer their services to their country now when the need is so great.

It must be made clear that we are not asking for physicians and dentists from areas where a shortage already exists. We are only trying to replace the physicians and dentists who have completed their obligation and who will be relieved from duty with the armed forces and will return to civilian life to practice their professions.

Your co-operation in this campaign can be of inestimable value and will be greatly appreciated by the medical departments of the armed forces, the young men and women in our armed forces and the families of these young people.

JAMES FORRESTAL

Office of the Secretary of Defense
Washington

BOOK REVIEWS

The Battle of the Conscience. A psychiatric study of the inner working of the conscience. By Edmund Bergler, M.D. 8°, cloth, 296 pp. Washington: Washington Institute of Medicine, 1948. \$3.75.

The title and subtitle of this work lead one to believe that here at last is a full-length study of a controversial and highly important subject. Instead, there are a number of related but, unfortunately, not fully integrated chapters — each almost complete in itself — in which the role of conscience is studied only as it pertains to the topic under discussion. Frequently, greater emphasis is placed on other studies of the author, with especial emphasis on the triad of the mechanism of oral erotism (as the basis for neurotic symptoms), and for sublimation a five-layer structure is alleged to exist.

Granting such possible mechanisms, one remains unimpressed about the designated numbers or strata as such. Clinical experience convinces one that such categories, although convenient, rarely exist, and this is not too strange since undoubtedly neither psychiatrist nor analyst ever succeeds in learning even an infinitesimal part of the dynamics of the mind (the thought process, the conscience) at either conscious or unconscious level.

Similar criticism can be made of the author's designation of magic gestures with completely different meanings. The fact that he designated various types under the term "magic gesture" will not succeed in preventing confusion in the literature because it is reasonable to assume that the term will be frequently used and its meaning will not always be clear.

An apology is made that analytical material is scant in criminal cases because some millionaire has failed to donate funds for such a study — a candid, but disheartening admission, when one recalls that scientists in other fields have devoted years of study without thought to monetary reward. This has been true particularly in the medical world and applies not only to research but also to care of the sick. Therefore, one might suppose that despite the lack of funds for 50 experienced analysts to devote themselves exclusively

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Dr Smart's observation that the British people like their new health service is hardly astounding when one considers that it purports to relieve them of all responsibility in connection with illness and that only a tiny fraction of the expense of this service is borne by the direct health-insurance contributions of the person himself. The tentative conclusion to which I came however was that the doctor's colossal load under these conditions precluded efficient action by him — nor does Dr Smart appear to challenge this.

He does condone grievous delays in vitally needed hospital construction even though patients on long waiting lists for admission to hospitals die in their homes before a hospital bed is available. He states "that the highest priority should be given to domestic building," because "nothing undermines domestic morale more than sharing a house with another family." For some time we in my family have been sharing our house with another couple and their children. Dr Smart will perhaps be relieved to learn that the morale of the entire *ménage* remains excellent, and if this arrangement has by any chance hastened the completion of the new buildings of the Massachusetts General Hospital and the New England Center Hospital we are that much happier.

WILLIAM H. SWEET

Boston

REGARDING THE FARREN HOSPITAL EPISODE

To the Editor With the summary administrative dismissal of 4 members of the Franklin District Medical Society from the medical staff of the Farren Memorial Hospital in Montague City, Massachusetts, in the three days before the election in November, 1943, a total of 20 doctors have lost their hospital privileges in western Massachusetts for publicly approving the "Birth Control" referendum on the Massachusetts ballot. The others were 12 in the Pittsfield area in 1942, and 4 in the Springfield area in 1946.

The first amendment to the constitution of the United States seems to guarantee the right of free speech without penalty, the citizens of Massachusetts in the same election overwhelmingly voted reapproval of this guarantee, the Massachusetts Supreme Court had certified this referendum to the ballot for public discussion and vote, and no promise, either written or oral, had ever been requested of any of these doctors before in connection with this amendment. The medical-staff by-laws have no such requirements. No hearing, either before or after dismissal, has ever been granted. No doctor has ever been reinstated except by signing a new application blank, which included a promise not to exercise this right of free speech, 4 doctors in the Pittsfield area have made this promise.

As president of the Franklin District Medical Society I held several consultations with the Sister Superior, and with 2 members of the Executive Committee of the Trustees, two committees of the Society held meetings during the month of November, one of them with the hospital authorities. An energetic petition supporting reinstatement was voted by the Society and presented to the Board of Trustees. In spite of this abridgment of civil rights the petition was not even placed on the agenda for the meeting by the President. A petition by me as a twenty-year member of the Farren Memorial Hospital medical staff and simultaneously president of the District Medical Society was sent to the Most Reverend A. G. Cicognani, the Apostolic Delegate in Washington, and its receipt has been doubly verified. With the passage of several weeks, even with a follow-up letter, no answer has been received.

anajes del Dispensario Antituberculoso Central y del Sanatorio Antituberculoso de Oira de Santa Cruz de Tenerife, Canarias, España. Director Dr T Cervia Volume VIII, Años 1946-47 8°, paper, 245 pp, illustrated Santa Cruz de Tenerife Imprenta Católica, 1948

This report is divided into two parts, the first comprising the statistics of the sanatorium for the years 1946 and 1947, and the second consisting of a series of clinical papers by Director Cervia and his assistants on the various aspects of tuberculosis. The text is concluded with a poem by Dr Duran, entitled *Cantar del buen bacilo*. The volume constitutes a valuable addition to the literature of tuberculosis, and the series should be in all collections on the subject and in reference and research medical libraries.

Textbook of Surgical Treatment, including Operative Surgery Edited by C F W Illingworth, CBE, MD, ChM, FRCS, Regius Professor of Surgery, University of Glasgow. Compiled by twenty-one contributors. Third edition. 8°, cloth, 644 pp, with 289 illustrations. Baltimore Williams and Wilkins Company, 1947 \$10 00

This collected work by twenty-one contributors has been revised and brought up to date. Four contributors have been added to the authors. The chapter on wounds and wound infections has been rewritten, and sections added on penicillin in surgery, plastic surgery, rehabilitation and facio-maxillary injuries. New material has been incorporated on the use of protein in surgery, the Rh factor and the anticoagulant treatment of thrombosis. Fifty-nine illustrations have been added. The work is of British origin and is well published in every way. It is recommended as a reference text for all medical libraries and surgeons.

Recent Advances in Surgery By Harold C Edwards, CBE, MS, FRCS, surgeon and lecturer in surgery, King's College Hospital, London, surgeon to the Evelina Hospital for Sick Children, and dean of the medical school, King's College Hospital. Third edition. 12°, cloth, 437 pp, with 131 illustrations. Philadelphia Blakiston Company, 1948 \$6 50

The first edition of this reference book was published in 1928, the second edition of 1929 was translated into Spanish, and this third edition has been revised to bring the material up to date. Short lists of references are appended to the various chapters. The material is well organized and is arranged by divisions of the body. Short lists of references are appended to the various chapters. It is a British book, printed in Great Britain, and well published. The plates are separately inserted in the text. The volume should be in all medical libraries and should prove useful to surgeons.

Oral and Dental Diseases. Aetiology, histopathology, clinical features and treatment. A textbook for dental students and a reference book for dental and medical practitioners By Hubert H Stones, MD, MDS, FDS, FRCS, Eng., professor of dental surgery and director of dental education, University of Liverpool, and consultant, E M S Maxillo-facial Centre, Broad Green Hospital, Liverpool. 8°, cloth, 896 pp, with 926 illustrations. Baltimore Williams and Wilkins Company, 1948 \$18 00

This volume constitutes a comprehensive treatise on the diseases of the mouth, jaws and teeth. The material is well organized. There is a long chapter on oral tumors and one on the diseases of the salivary and oral mucous glands. Lists of references are appended to the various chapters. The text is well printed with a good legible type. Comprehensive indexes of authors and subjects conclude the volume. The treatise is British and printed in Great Britain. It is recommended for all medical libraries and should prove valuable to all dentists and to physicians interested in the subject.

Retropubic Urinary Surgery By Terence Millin, MA, MCh (DUBL), FRCS, FRCSI, surgeon, All Saints' Hospital for Genito-Urinary Diseases, London, genitourinary surgeon, Royal Masonic Hospital, London, urologist, Surrey County Council, and genitourinary surgeon, Chelsea Hospital

for Women, London, Southall-Norwood and Cray Valley hospitals. 8°, cloth, 208 pp, and 163 illustrations. Baltimore Williams and Wilkins Company, 1947 \$7 00

This monograph describes the author's methods of retro-pubic approach for prostatic surgery. Included is his hitherto unpublished operation for stress incontinence in women, first used in 1944. An appendix lists fifty consecutive one-stage retropubic prostatectomies. A good index ends the text. The book is of British origin and is well published. It should prove valuable to all surgeons interested in the subject.

A Course in Practical Therapeutics By Martin E Rehfuess, MD, professor of clinical medicine and Sutherland M Prevost Lecturer in Therapeutics, Jefferson Medical College Philadelphia, and attending physician, Jefferson Medical College Hospital, Philadelphia, F Kenneth Albrecht, MD, and Alison H Price, MD, assistant professor of medicine, Jefferson Medical College, Philadelphia, and assistant physician, Jefferson Medical College Hospital, Philadelphia. 4°, cloth \$24 pp, with 70 plates. Baltimore Williams and Wilkins Company, 1948 \$15 00

This joint work of thirteen clinicians covers the whole field of therapeutics in a practical manner. The text is divided into four large sections comprising general therapeutic principles, symptomatic therapy, treatment of specific disorders and special treatment. The symptoms discussed in the second part are arranged alphabetically. The various diseases and conditions in the third part are arranged by the systems of the body or by classes of diseases. The treatment of each disease is preceded by a concise description of the etiology, pathology and symptomatology. The treatment is extensive in scope. The material is well arranged, and the text is well printed with a good type in two columns on good paper. A comprehensive index concludes the volume. The inside front and back covers are used for valuable tables on normal values in blood constituents and metric and apothecary doses. This is a poor practice because anything printed on the covers becomes defaced and worn from usage of the volume. The book should prove valuable to physicians in their daily work, and as a reference work for medical libraries.

Human Nutrition By V H Mottram, MA (Cant.) 12°, cloth, 151 pp, with 9 illustrations. Baltimore Williams and Wilkins Company, 1948 \$2 75

This popular manual on human nutrition is written by an eminent British scientist. The material is well arranged and written in a simple, easy style. The fundamentals of dietetics, food hygiene and cooking and processing and storage of foods and proteins, minerals and the vitamins are considered in various chapters. There are also chapters on normal dietetics, digestion, absorption and metabolism of food, and on the nature of foods, comprising analyses of the common foods. The chapter on the optimal diet is gauged to present British conditions. A good index concludes the text. The volume is well published.

Treatment by Manipulation in General and Consulting Practice By A G T Fisher, MC, MB, ChB, FRCS (Eng.), orthopedic surgeon to the rheumatic unit, St. Stephen's Hospital. Fifth edition of *Manipulative Surgery*. 8°, cloth, 275 pp, with 126 illustrations. New York Paul B Hoeber, Incorporated, 1948 \$5 00

This book was first published in 1925 under the title of *Manipulative Surgery*. In this fifth edition much material has been added, and forty-five new illustrations have been included. Many sections have been rewritten and expanded to incorporate the advances in knowledge made since the fourth edition of 1944. Emphasis has been placed on the treatment of crippling deformities of rheumatic disease. The objective of the work is to emphasize the value of manipulative treatment in carefully selected cases of certain sequelae of injuries and diseases affecting the joints, muscles, tendons and fasciae. The various chapters discuss the pathology of the joints, prevention and diagnosis of adhesions and manipulative treatment in general and of the upper and lower extremities, the spine and the sacroiliac joint. The concluding chapters consider the dangers of manipulation in unsuitable cases, after-treatment and osteopathy. The book is of British origin and printed in Great Britain. The publishing is well done, and the illustrations are excellent. The volume should be in all medical libraries and should prove useful to orthopedists.

to the study of criminals, perhaps each analyst might feel honored to participate in such a study by devoting a "free hour" to the purpose.

Apart from these few criticisms, the book makes good reading, the examples cited are typical, and sources of other works are clearly acknowledged. The author's style remains clear, but by now, this is taken for granted in any of Dr. Bergler's books.

The Driving Forces of Human Nature and Their Adjustment: An introduction to the psychology and psychopathology of emotional behavior and volitional control. By Thomas V. Moore, Ph.D., M.D. 8°, cloth, 461 pp., with 26 illustrations. New York: Grune and Stratton, 1948. \$6.50.

In this work the author presents a compilation of some of the more important aspects that are at present acceptable in the study of the forces concerned in human behavior. The author draws upon his obviously extensive and broad cultural background to clarify his position, and colors the entire work with a religious (Roman Catholic) texture. It is in essence a psychologic, philosophical work in which he draws upon examples both in experimental psychology and in psychiatric therapy. He touches on various theories concerned in the dynamics of human behavior and, for the most part, maintains a "middle of the road" position regarding dynamic theories, reserving as his ultimate solution that of religion. He presents numerous case studies and methods of treatment concerning these cases, choosing them carefully to illustrate his point of view. As an introduction to the problems of human nature, the book presents a wealth of material both historically and analytically.

Physiology of Exercise. By Laurence E. Morehouse, Ph.D., and Augustus T. Miller, Jr., Ph.D. 8°, cloth, 353 pp., with 51 illustrations and 10 tables. St. Louis: C. V. Mosby Company, 1948. \$4.75.

This book attempts to give the fundamental facts of physiology as they concern exercise. It is written primarily for teachers of physical education and practitioners of physical medicine. The material is presented in a simple, easily understood style. A glossary at the end of the book explains the technical terms that have been used. The chapters on physical fitness and on training should be of particular interest to physicians. This book can be recommended as a helpful volume containing the essential data on the physiology of exercise.

Psychic Energy: Its source and goal. By M. Esther Harding, M.D., M.R.C.P. With a foreword by C. G. Jung. 8°, cloth, 497 pp., with 5 illustrations and 9 plates. New York: Pantheon Books, 1947. \$4.50. The Bollingen Series X.

In this book the author, via a Jungian delving into the "unconscious," attempts to answer the query whether or not the primitive and "unconscious" side of man's nature can be tamed effectively or even altered. She believes that contemporary culture and civilization afford but a poor façade covering unconscious roots that are essentially base, vile and self-annihilating. Such a façade is superficial and vulnerable, and men must regress to primitive levels of the unconscious, as seen in the totalitarian rationalization and the world conflicts of today. The author holds out little hope of changing the "collective unconscious" of a people, but individuals may be saved and thus possess "the germ of a renaissance of the spiritual values of mankind."

The author draws freely upon the art and literature of various cultures in support of her theses, but this seems to serve only the more to leave the reader with the sensation of having viewed a séance of religious mysticism. The book is as pessimistic and ethereal as anything Jung himself might have written. One gathers that peoples, as such, are doomed, condemned even pre-partum by the "collective unconscious"; salvation there is for an accidental few who can be led, through the means of "analytical psychology," to wallow in the "unconscious" and be led therefrom again chaste and pure in heart and mind.

BOOKS RECEIVED

The receipt of the following books is acknowledged and this listing must be regarded as a sufficient receipt for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

De betekenis van de lymfklier-punctie voor de diagnostiek periferie lymfklierzwellingen. By L. B. J. Stuyt. Ar. Proefschrift, Universiteit van Amsterdam, 1 Juli, 1947. paper, 110 pp., with 31 illustrations. Amsterdam: S. & H. H. Holkema's Boekhandel, 1947.

In this monograph, which was presented as a thesis for the degree of doctor of medicine at the University of Amsterdam in 1947, the author discusses puncture and aspiration of swollen lymph nodes for the purpose of obtaining material for cytologic diagnosis. The text is based on the experience of the author with over 300 patients and on the literature of the subject. The author indicates that the method may be used when biopsy is contradicted, that it is possible to identify cell pictures in a number of conditions and that the procedure may be used as often as desired and as a control on therapy, he recommends that the method be adopted as routine in the differential diagnosis of enlargement of the peripheral lymph nodes. The material is well organized, discussing in order the anatomy and physiology of the lymph nodes, and their pathological anatomy, the clinical diagnosis of enlargement of the peripheral lymph nodes, the technique of puncture and its diagnostic value. The text is in Dutch, with summaries in English and French. A bibliography is appended to the text. The type, printing and illustrations are excellent.

Racial Variations in Immunity to Syphilis: A study of the disease in the Chinese, white and Negro races. By Chester N. Frazier, M.D., Dr. P.H., and Li Hung-Chung, M.D. 8°, cloth, 122 pp., with 27 tables. Chicago: University of Chicago Press, 1948. \$2.50.

In this monograph the authors analyze 16,845 consecutive cases of syphilis in the Chinese, white and Negro races. The study points out that regardless of race or sex the disease was essentially the same in all people and that the differences between races lay almost entirely in the relative frequency of the development of the disease. A bibliography and a good index conclude the volume.

Advances in Pediatrics. Editorial Board: S. Z. Levine, M.D., Cornell University Medical College, New York; Allan M. Butler, M.D., Harvard Medical School, Boston; L. Emmett Holt, Jr., M.D., New York University, College of Medicine, New York; and A. Ashley Weech, M.D., University of Cincinnati, College of Medicine, Cincinnati. Volume III. 8°, cloth, 363 pp. New York: Interscience Publishers, 1948. \$7.50.

This third volume of an important series presents eight papers by different authors of interest to pediatricians and physicians concerned with the diseases of children. The papers comprise the effects of birth processes and obstetric procedures upon the newborn infant, retrolental fibroplasia, emotions and symptoms in pediatric practice, therapeutics of epileptiform seizures, viral hepatitis, abnormalities of sexual development during childhood and adolescence, psychologic considerations of puberty and adolescence, and the osteochondroses. The papers present the up-to-date knowledge on the particular subjects under consideration. Comprehensive bibliographies are appended to the various papers. There are good indexes of authors and subjects and the volume is concluded with a cumulative index of authors and subjects for volumes 1 to 3. The type and printing are good, but a heavy, coated paper is unnecessarily used, making the volume too heavy for its size. It should be remembered that when this type of paper becomes wet by accident the volume is transposed into a block as hard as concrete. The series is valuable and should be in all medical libraries and in the collections of physicians interested in pediatrics.

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CARDIAC ANEURYSM*

MAX CAPLAN, M.D.,† AND PAUL M. SHERWOOD, M.D.‡

ROCKY HILL, CONNECTICUT

PRIOR to 1931, the diagnosis of acquired aneurysm of the left ventricle was made only ten times ante mortem^{1,2} With the better appreciation of the significance of the clinical features of this condition and the increased use of modern diagnostic facilities, more and more cases have been reported in the literature, and a new evaluation of the prognosis is warranted. Thus, although in Parkinson, Bedford, and Thomson's³ cases, the longest survival was thirty months, in Dressler and Pfeiffer's⁴ cases it was seven years. Young and Schwedel⁵ have reported the case of a patient who survived for ten years after the diagnosis of cardiac aneurysm, and Penner and Peters⁶ described a patient who, up to 1946, had already survived fifteen years. Many cases have been reported in which the patients have pursued a useful and comparatively active life for two, four, five,³ seven^{4,7} and nine⁷ years after the development of the characteristic radiographic findings of ventricular aneurysm. The longest survival mentioned in the literature is a patient, followed by Robertson⁸ for eighteen years, who still engages in heavy work. Formerly a rare condition, ventricular aneurysm is now frequently suspected before death and no longer, by itself, has the dire prognosis commonly associated with it in the past.^{3,9} We report herewith 2 cases of cardiac aneurysm followed on the Medical Service of the Veterans Home and Hospital at Rocky Hill, Connecticut.

CASE REPORTS

CASE 1 W. C., a 56-year-old man, was transferred to the hospital for convalescent hospital care. He was a highway-department maintenance worker, and his duties had included pick and shovel work as well as clearing snow. From 1943 to 1946 he had noted occasional sharp stabbing nonradiating pains in the anterior portion of the chest deep behind the lower third of the sternum. The onset was sudden and usually occurred while he was at work; the pain waxed and waned and varied in duration from several hours to an entire day. On the evening of June 20, 1946 he was suddenly seized with severe substernal and precordial pain, which radiated down both arms. He was immediately sent to a hospital. Two weeks later and again 4 weeks later, while in the hospital he had a similar but much milder episode

of substernal pain. Thereafter he improved uneventfully and was transferred to this hospital.

Physical examination revealed a well developed and well nourished man who was not acutely ill. Examination of the head was not significant. The thyroid gland was not enlarged. The lungs were clear. The maximum cardiac impulse was heaving and appeared in the fourth interspace just medial to and below the left nipple and 2 cm. inside the left border of cardiac dullness. The heart sounds were distant and faint, and not in keeping with such a marked cardiac pulsation. Rhythm was regular, and no murmurs were present. The liver was not enlarged, and there was no peripheral edema.

The blood pressure was 136/84 in both arms.

Laboratory examination revealed normal urine specimens and no anemia or leukocytosis, the nonprotein nitrogen was 29, and the fasting blood sugar 103 mg. per 100 cc. and the sedimentation rate was 12 mm. per hour (Cutler method). Blood Wassermann and Mazzini tests were negative.

X-ray examination of the chest disclosed the heart to be somewhat enlarged in the transverse diameter and revealed a marked prominence and dilatation of the left border of the heart (Fig. 1). Under the fluoroscopic screen, an expanding pulsation of the bulging area that coincided with each contraction of the left ventricle was noted.

An electrocardiogram (Fig. 2) showed regular sinus rhythm, with a rate of 80, a PR interval of 0.20 second and QRS complexes of 0.08. In Lead I the main deflection was downward, with elevated, bowed ST segments and a shallow, inverted T wave. The R wave was notched and the T wave, low and upright in Lead 2. Lead 3 showed depressed ST segments. In the left-arm lead the main deflection was downward, with elevated, bowed ST segments, and a shallow, inverted T wave. The right-arm lead had an inverted P wave, upright QRS complexes and a diaphasic T wave. In the left-leg lead the QRS complexes and T wave were upright. The R waves were low in Lead V₁ and absent in Leads V₂, V₃, V₄ and V₅, the ST segments were elevated in Leads V₂, V₃, V₄ and V₅, and the T waves were diaphasic in Lead V₂ and inverted in Leads V₃, V₄ and V₅. In Lead V₆ there were low-voltage QRS complexes, elevated ST segments and an inverted T wave. Serial electrocardiograms showed no essential change.

The patient has been fully ambulatory in the hospital and has cared for himself completely. He walks to the dining room and to the auditorium for motion-picture entertainment. He performs light work at the Department of Occupational Therapy. In addition, he voluntarily helps in small tasks about the ward. His complaints referable to the cardiovascular system are limited to palpitation after infrequent climbing of stairs. Repeated x-ray films over the two-year period while he has been in this hospital have revealed no change in the size or configuration of the heart (Fig. 1).

CASE 2 A. S., a 74-year-old man, was admitted to the hospital on July 9, 1948, because of shortness of breath. Nine months before admission, directly after arising from bed he had suddenly been seized with excruciating pain in the left anterior portion of the chest. There was associated sweating and marked shortness of breath. He entered another hospital, where on the following day the precordial pain was more pronounced. His pulse was stated to be rapid

*From the Medical Service, Veterans Home and Hospital.

†Attending physician, Veterans Home and Hospital, chief of medicine, Meriden Hospital, Meriden, Connecticut.

‡Staff physician, Veterans Home and Hospital.

Textbook of Chiropody By Margaret J M Swanson, B Litt, F Ch S, co-founder of Edinburgh Foot Clinic and School of Chiropody 8°, cloth, 212 pp, with 168 illustrations Baltimore Williams and Wilkins Company, 1948 \$5 00

This short treatise on chiropody as a specialty also considers the medical and surgical conditions met with in practice that should be referred to competent specialists. The text is well written in a scientific manner, and the material is well arranged. The publishing is excellent and was done in Great Britain. The illustrations are also excellent. A glossary of terms concludes the text. There is a good index. The book is recommended to medical libraries and to all persons interested in the subject.

Principles and Practice of the Rorschach Personality Test By W Mons, M R C S, L R C P, Lt-Col R A M C, adviser in psychiatry, South East Asia Command 8°, cloth, 164 pp Philadelphia J B Lippincott Company, 1948 \$4 00

This manual on the Rorschach ink-blot test is intended as an introduction to more advanced works and is based on ten years' experience, including examination of 1000 children, aged four to sixteen years, and divided into two equal groups of normal and subnormal children. There is a good index, and the publishing is excellent in every way.

Standards for the Diagnosis and Treatment of Cancer By the Cancer Committee of the Iowa State Medical Society 8°, paper, 160 pp Iowa City, Iowa Athens Press, 1948 \$1 00

This manual was first published in 1937. During the following eleven years over fifty thousand copies were printed and distributed to the medical profession of Iowa and nearby states. This second edition has been revised to bring the subject up to date. The text is divided into a number of short, concise chapters on the diagnosis, treatment and prognosis of cancer of the various organs and structures of the body. Under diagnosis the early and late signs and differential diagnosis are considered. Two preliminary chapters discuss general considerations and the cancer problem and the family doctor. The final chapter is on radiation therapy in general. An extensive bibliography arranged by chapters concludes the text. The manual is well published in every way and should prove valuable as a compendium for practicing physicians.

Microbiology and Pathology By Charles F Carter, M D, instructor in pathology and applied microbiology, Parkland Hospital School of Nursing, Dallas, Texas, director, Carter's Clinical Laboratory, Dallas, consulting pathologist, St Louis Southwestern Railway Hospital, Texarkana, Arkansas, and consulting pathologist, Mother Frances Hospital, Tyler, Texas. Fourth edition 8°, cloth, 845 pp, with 216 illustrations St. Louis C V Mosby Company, 1948 \$5 00

Dr Carter, in this new edition of his standard textbook, first published in 1936, has thoroughly revised the text to bring it up to date. The section on microbiology has been entirely rewritten, incorporating the great advances in knowledge in the field since the publication of the third edition in 1944, including the use of the sulfonamides and the antibiotics. A chapter on immunization has been added. The section on pathology has been largely rearranged and rewritten. Infectious hepatitis and homologous serum jaundice have been discussed, and new chapters on the hospital pathologist and his work, and on defects of body development have been included. Lists of selected references have been appended to the various chapters. The text is concluded with a chapter on laboratory exercises and a glossary of terms. There is a good index. The book is designed for the use of schools of nursing and nurses, and the need of four editions speaks well for its soundness.

Preoperative and Postoperative Care of Surgical Patients By Hugh C Ilgenfritz, M D With a foreword by Urban Maes, M D, D Sc. 8°, cloth, 898 pp, with 110 illustrations St. Louis C V Mosby Company, 1948 \$10 00

This treatise is comprehensive in scope. The early chapters deal with general subjects such as fluid and electrolyte balance, metabolism and nutrition, shock, transfusion sedative

medication, systemic and organic complicating factors, therapy, general measures, minor and major postoperative complications, care of the wound and burns. The later chapters consider the various organs and regions of the body. A comprehensive index concludes the volume. The type printing is excellent, but the use of a heavy filled page is not justified by the text. The book should prove useful to surgeons and as a reference work for medical libraries.

More Than Armies. The story of Edward H Cary, M D Booth Mooney With an introduction by Dr Morris Wein 8°, cloth, 270 pp Dallas, Texas Mathis, Van and Company, 1948 \$5 00

This biography of Dr Cary is written in a narrative by a trained journalist. Dr Cary has been interested in medical education for many years and has been closely associated with the American Medical Association for thirty years, serving as trustee for five years and as president of the Association in 1933. He is a past president of the Southern Medical Association. He served for a number of years as dean of the Medical School of Baylor University and, in 1917, founded the Southwestern Medical College. He is a distinguished ophthalmologist. The book is well published, but lack of chapter headings detracts from its reference value and the price of five dollars seems high for the volume. It is recommended for all medical-history collections.

Take Off Your Mask By Ludwig Eidelberg, M D 8°, cloth, 230 pp New York International Universities Press, 1948 \$3 25

This small volume depicts an imaginary working day of a psychoanalyst. Seven case histories are presented, dealing with different kinds of psychic disturbance. These cases are not actual but are built up to portray ideal examples of condition under discussion. One chapter is devoted to training analysis. The book is semipopular and should prove useful to persons interested in the subject.

Eskimo Doctor By Aage Gilberg, M D Translated by Elliott 8°, cloth, 229 pp, illustrated New York W W Norton and Company, Incorporated, 1948 \$3 00

This is the story of a young Danish physician who went to be the community doctor for an isolated group of polar Eskimos in Thule, Greenland, the northernmost human settlement in the world. Dr Gilberg tells of the day-to-day life of himself and his wife, describing his adventures while he ministered to the people scattered over a large area, and the character and customs of the Eskimos. The story is well told in an easy, narrative style. The book is translated from the original Danish. It is recommended for all medical history collections and to all persons interested in the history of medicine. It is a fine piece of work.

NOTICES

MASSACHUSETTS ASSOCIATION OF MEDICAL TECHNOLOGISTS

The state conference of the Massachusetts Association of Medical Technologists will be held at Horticultural Hall, Elm and Chestnut Streets, Worcester, on Saturday, April 17.

PROGRAM

- 10 00 a m - 12 00 m Business meeting and nomination of state officers (Mrs. Eichman of the American Society of Medical Technologists, will be the speaker)
- 12 30 p m Lunch
- 2 00 - 3 00 p m Newer Serologic Technics for Isoantibodies Dr Victor Vaughan, III
- 3 00 - 4 00 p m Registry Its standards and how to establish them Dr Donald Nickerson

(Notices concluded on page xv)

were heard. The blood pressure in both arms was 150/90. The liver was enlarged and tender, and pitting edema of both ankles was present.

Laboratory examination disclosed negative urinalyses and no anemia or leukocytosis. The blood Mazzini test was negative.

X-ray examination of the chest revealed considerable cardiac enlargement. Projecting upward from the left ven-

ward) and upright T wave. The left-leg lead showed a tall R wave, deep S wave, depressed ST segments and upright T wave. Lead V_1 showed a small R wave, deep S wave and upright T wave, with U wave present. Lead V_2 showed deep QS complex and upright T wave, with U wave present. In Lead V_3 the QS complex was present, with embryonal R wave and upright T wave. In Lead V_4 the QS complex

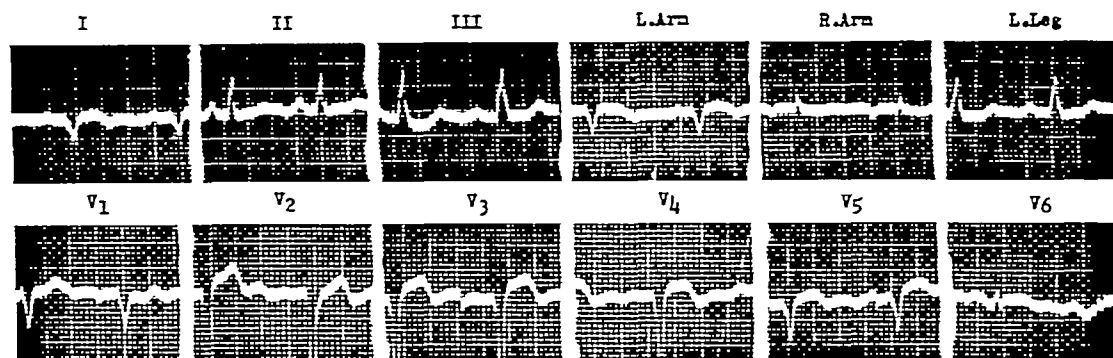


FIGURE 2 *Electrocardiogram in Case 1*

tricular contour there was a bulge extending for a distance of approximately 4 cm. The base of the bulge measured 8 cm in diameter (Fig. 3).

An electrocardiogram (Fig. 4) showed regular sinus rhythm, with a rate of 94, a PR interval of 0.18 second and QRS complexes of 0.10. The Q wave was deep in Lead I. The R waves were tall in Leads 1, 2 and 3. The ST segments were ele-

vated, with embryonal R wave, elevated ST segments and diphasic T wave. In Lead V_3 the Q wave was small, the ST segments elevated, and the T wave diphasic. The ST segments were elevated and bowed in Lead V_4 , with a shallow, inverted T wave.

On a low-salt diet, digitalization, and mercurial diuretics, the patient rapidly improved and has become asymptomatic.

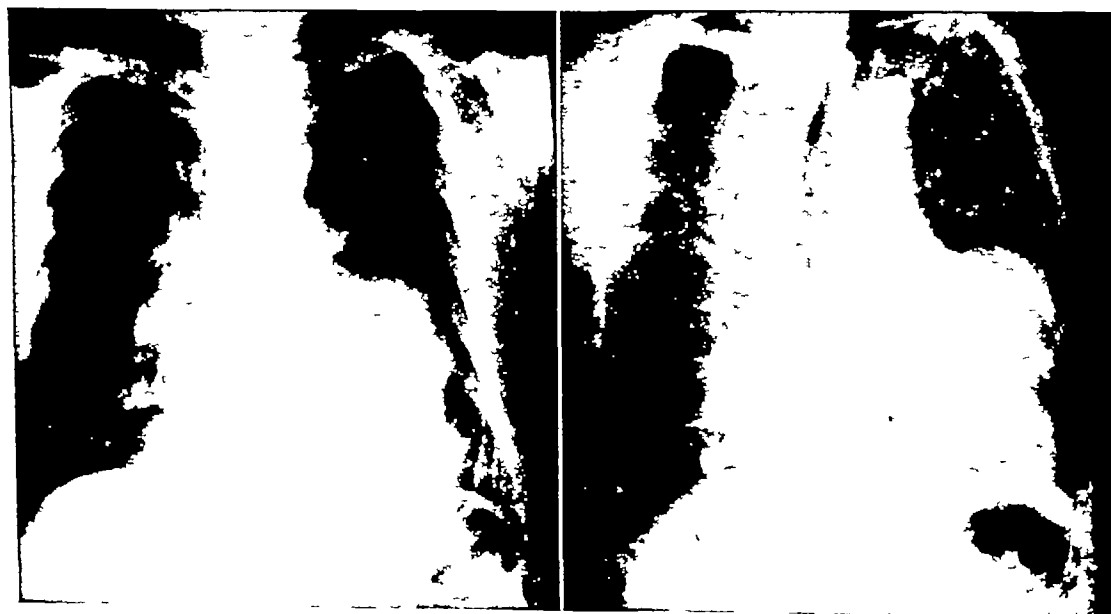


FIGURE 3 *Roentgenograms in Case 2*

The photograph on the left shows the anteroposterior view, and that on the right the right oblique view.

vated in Lead I slightly depressed in Lead 2 and depressed in Lead 3. The T waves were inverted in Lead 1 and upright in Leads 2 and 3. The S waves were deep in Leads 2 and 3. The left-arm lead showed a deep Q wave, tall R wave, elevated ST segments and inverted T wave, and the right-arm lead small QS complex (main deflection down-

The rales and peripheral edema disappeared, and the liver is no longer palpable. He is fully ambulatory in the hospital and is employed by the Department of Rehabilitation as an elevator operator. He has been entirely asymptomatic except for a transient episode of faintness, which occurred after he had climbed a flight of stairs.

and weak, and his temperature rose to 103.6° . The white-cell count was 16,800 and an electrocardiogram showed "myocardial damage, coronary closure, and sinus tachycardia." He had severe anginal pain when moved. He gradually improved and was discharged in February, 1948. He

His dyspnea had returned and was becoming progressively worse. His appetite was poor, and nocturia was present.

Physical examination revealed an elderly man in no distress. The fundi were Grade I and hypertensive-arteriosclerotic. The thyroid gland was not enlarged. There was



FIGURE 1 Roentgenograms in Case 1

The left upper photograph shows the anteroposterior view, the right upper the right oblique view (taken in November, 1946), the left lower the right oblique view (taken in March, 1948), and the right lower the left lateral view.

was rehospitalized 1 month later for congestive failure and improved on digitalization. At this time x-ray films were interpreted as showing "cardiac enlargement with a question of aneurysm." He was discharged to a convalescent home in April, 1948. In July the patient was admitted to this hospital

no distention of the neck veins. There were scattered crepitant rales at both lung bases. The point of maximal impulse was diffuse and forceful but displaced above the left nipple and inside the midclavicular line. The heart sounds were distant. The rhythm was regular, and no murmurs

Cardiac aneurysms have been described as varying from the size of a small prune,¹⁹ or a large duck's egg,²⁰⁻²² to an area equal to or greater than the heart itself.²⁰⁻²² Sternberg¹³ includes small, clot-containing cavities wholly within the cardiac wall as aneurysms, and states that thus many cardiac aneurysms are present that do not distort the cardiac contour. The average measurements of the cardiac aneurysm as observed in 21 cases at autopsy were 2 to 4 cm in diameter and 1.2 to 3 cm in depth.²⁻¹⁶ In the living patient, however, the apparent size of the aneurysm is greater, owing to the increased intracardiac pressure during systole. The aneurysm may be noted over a period to increase in size. Cardiac aneurysms are not infrequently multiple, and in the series of 21 cases described by Brams and Gropper¹⁵ in which the aneurysm was found at autopsy, 6 had two or more such aneurysms.

Incidence

Aneurysm of the heart is stated by Parkinson, Bedford and Thomson² to occur in 9 per cent of patients suffering myocardial infarction. At the Massachusetts General Hospital in a series of autopsy cases examined between 1926 and 1945 Wang, Bland and White²⁴ found 52 large cardiac aneurysms in 556 patients with myocardial infarction, or an incidence of 10 per cent. An incidence of 10 per cent is also reported by Foord¹⁹ in 107 cases of old myocardial infarction. It is interesting to observe that although these three papers are based on series in three widely separated geographical areas (England, Massachusetts and California) the relative percentage is the same. Others have found the incidence even higher.²⁵ Libman²⁶ points out that cardiac aneurysm occurs fifteen times as frequently as Hodgkin's disease. With the increased diagnosis of myocardial infarction,²⁴ it is evident that cardiac aneurysm should be recognized oftener during life.

The development of the aneurysm closely follows the occurrence of myocardial infarction, many appearing within a week to several months after the acute episode.¹⁵⁻¹⁷ It is obvious, therefore, that the age incidence for cardiac aneurysm parallels that of myocardial infarction.

Since the incidence of myocardial infarction is greater in men than in women, it is likewise not surprising to note Crawford's² statement that in a summary of the literature, 66 per cent of patients with cardiac aneurysms were males. In later papers, the incidence in males appears higher. Parkinson et al.² (1938) report 14 out of 15, Brams and Gropper¹⁵ (1940) 20 out of 21, and Crawford² (1943) 11 out of 13.

CLINICAL FEATURES

Symptoms

Practically all the symptoms in patients with cardiac aneurysms can be attributed to the underlying cardiac lesion. The aneurysm per se is asymptomatic except for occasional development of pain in the region of the apex.²³ The anginal syndrome or symptoms of left ventricular failure that may appear are not produced by the aneurysm but are related to the coronary artery or myocardial disease. Patients who have had so-called silent myocardial infarcts may develop cardiac aneurysms without any symptoms whatsoever.

Physical Signs

Some signs are described that make one suspect the existence of this lesion. On inspection a pulsation that is plainly distinguishable from that of the apical beat is seen. This is forceful and heaving and is located just lateral to the left sternal border. With palpation, one may confirm the forcefulness and heaving character of the pulsation. Crawford² considers this sign of such importance that he states that its presence permits the diagnosis to be made by physical examination alone. The area of cardiac dullness is increased and sometimes is irregular in contour.

The heart sounds are usually diminished, but more characteristic is the 'dull first heart sound with poor tone with little or no muscular quality.'²⁷ This sign together with abnormal pulsation, was described by Libman²⁶ in 1926 as being highly suggestive of the diagnosis of cardiac aneurysm. Others have concurred in the importance of these physical findings. Brams and Gropper¹⁵ found pulsation present in 57 per cent of their 21 cases. Although not of diagnostic importance, other physical findings in cardiac aneurysm are a systolic murmur in the area of abnormal pulsation, which develops after a myocardial infarction and a gallop rhythm. The mechanism of the gallop rhythm found in a case of ventricular aneurysm was studied in detail by LeRoy and Roberts²⁸ who found that during systole the aneurysm bulged outward and by traction on the papillary muscle prevented the closure of the anterior leaflet of the mitral valve, resulting in auricular reflux of blood and producing a third heart sound.

The various arrhythmias that occur in severe myocardial disease are found in patients with cardiac aneurysm, and frequent extrasystoles, auricular fibrillation, auricular flutter and paroxysmal ventricular tachycardia have been described.³

A noteworthy feature of the clinical picture of cardiac aneurysm is the normal or low blood pressure. In a series of 15 cases,³ no evidence of previous or present hypertension was found. In Crawford's² series of 13 cases, only 1 patient showed elevated

ETIOLOGY

Pathogenesis

Although a small number of cardiac aneurysms are of rheumatic,^{8, 9, 10} syphilitic,^{1, 3} congenital,^{3, 10, 12} traumatic^{9, 10} and mycotic^{3, 9, 10} origin, the vast majority (at least 85 per cent)^{12, 14} follow coronary occlusion with subsequent myocardial infarction. The infarct is followed by necrosis, which in turn leads to connective-tissue scarring. A variable number of subendocardial elastic fibers are involved. The damaged area behaves in an abnormal manner in that for a period intracardiac pressure during systole results in its expansion. If sufficient fibrous tissue replaces the muscular elements, a localized

which cardiac aneurysm followed gumma or infective endocarditis and abscess formation

Site

Since most cardiac aneurysms follow myocardial infarction,^{13, 14} the most frequent locations for ventricular aneurysms are the areas supplied by the anterior descending branch of the left coronary artery — namely, the apex, the anterior wall of the left ventricle and the anterior half of the interventricular septum. Aneurysm of the posterior wall is rare^{3, 10} despite the frequency of posterior myocardial infarction, and to our knowledge has only been reported as diagnosed clinically by one author.¹⁷ Although aneurysm of the interventricular septum

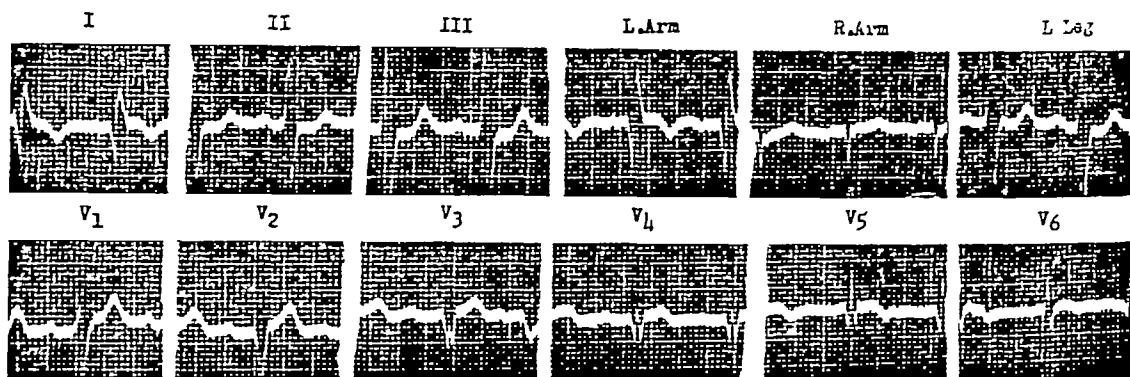


FIGURE 4 *Electrocardiogram in Case 2*

protrusion of the scar results. This protrusion, when present over a considerable length of time, becomes the chronic ventricular aneurysm. If the connective-tissue scar is not sufficiently strong to withstand the intracardiac pressures, rupture of the ventricle and death follow.

The factors that influence the integrity of the fibrous-tissue scar within the damaged area have been described as the number of attacks of myocardial infarction¹⁵ and the amount of bed rest after the acute episode.^{10, 14, 16} Other conditions, such as the presence of concomitant acute disease with increased demands on the heart, chronic pulmonary disease and lack of optimal therapy (oxygen), also affect the status of the healing cardiac musculature. The assumption that multiple attacks of myocardial infarction must occur before a cardiac aneurysm develops is unwarranted, since in 13 of 21 patients described by Brams and Gropper¹⁶ there was a history of only one acute episode.

Other etiologic mechanisms should not be overlooked. Linck¹¹ reports a case due to congenital origin of the left coronary artery from the pulmonary artery, a few cases have been described⁹ in

may cause a Bernheim syndrome⁹ and lead to its discovery by apparent right ventricular enlargement, in most cases this condition cannot be diagnosed during life.

Pathology

The shape of the aneurysm is variable. The most common type is merely a simple outpouching of the heart-muscle wall not sharply delineated from the remainder of the ventricle, occasionally, it is saccular and communicates with the ventricular cavity by means of a neck. The wall of the aneurysm is thin and occasionally transparent, and composed of replacement fibrous tissue and whatever muscular elements remain. It is covered by the firmly adherent pericardium. Within the aneurysm, thrombosis and eventually organization of the clot occur. Calcification of the wall, the clot or the pericardium occurs and may suggest the diagnosis roentgenologically. This calcification occurred in 30 per cent of 20 cases of ventricular aneurysm reported by Foord.¹⁸ It should be noted that calcification of the pericardium may occur as an independent entity, and its presence is not a specific radiographic finding of cardiac aneurysm.

Cardiac aneurysm is defined as a localized dilatation of the heart wall, usually as a result of a myocardial infarction. The size of the aneurysm may vary from the size of an egg, to an area the size of a fist. Sternberg^{20, 23} has reported that the aneurysms are usually of the ventricular type, and that they are often multiple. The average size of the aneurysm is 2 to 4 cm in diameter and 1 to 2 cm in depth.^{2, 16} In the living, the apparent size of the aneurysm is increased by the increased intracardiac pressure. The aneurysm may be noted on the roentgenogram as a localized increase in size. Cardiac aneurysms are frequently multiple, and in the case described by Brams and Groppe¹⁶ an aneurysm was found at autopsy, such aneurysms

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associated with pulmonary hypertension, it enlarges the conus arteriosus so that it is difficult to detect a diastolic aneurysm. Carefully performed roentgenograms will demonstrate that the area involved is the entire pulmonary conus rather than a localized ventricular bulge, and the type of murmur (in cases of mitral stenosis), the history of congenital heart disease or signs of congestive heart failure aid in this differentiation.

Lesions that produce apparent enlargement of the cardiac silhouette and may be confused with a cardiac aneurysm are tumors of the lung. Of these, dermoids occur at the periphery and are usually asymptomatic except for respiratory symptoms, and there is no antecedent history of myocardial infarction. Some contain teeth or other bony structures. Seen on x-ray examination, a teratoma of the diaphragm may distort the cardiac silhouette but may be associated with teratomas in the ovary or testis.

Other malignant intrathoracic tumors may be confused with a cardiac aneurysm but may be confusing when in the region of the ventricular shadow.²⁶ With the use of the technic of visualization of the heart by contrast dyes and related structures by contrast media, 100 per cent diodrast solution most lesions can be delineated.

A localized bulge of the pericardium projects to the right of the usual left-sided cardiac silhouette. A cyst of the pericardium can be differentiated by appropriate skin and serologic studies. A pericardial fat triangle is easily differentiated from a cardiac aneurysm.

A cardiac aneurysm does not in itself have a benign course. The underlying cause is the existence of the aneurysm, not the development of anginal pain, edema, or congestive heart failure, or death. Recurrent acute episodes may be attributed to the cardiac aneurysm. A progressive coronary-artery disease. Fisher²⁸ has recently reported a case of ventricular aneurysm with rupture. He grafted a segment of fascia lata over the aneurysm in the hope of preventing

ETIOLOGY

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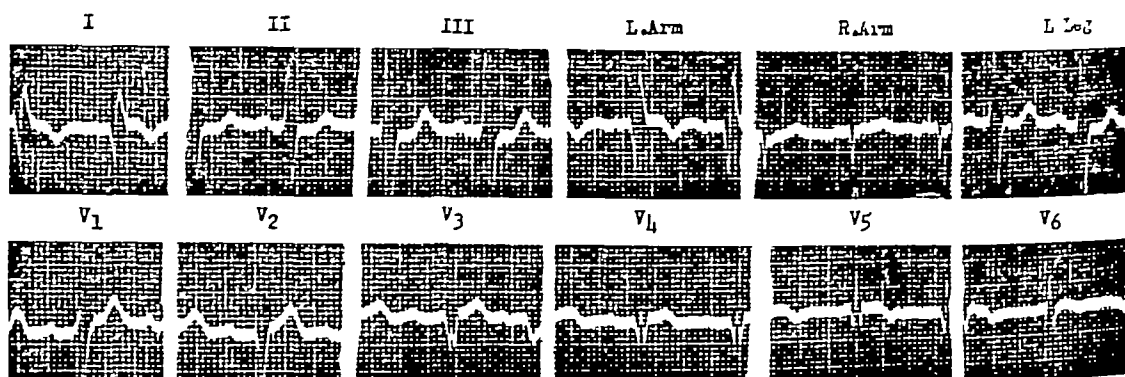


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sequent involvement of the pleura or diaphragm. This systolic expansion is one of the bases for the diagnosis by roentgenkymography. Absent pulsation in this area is the other.

Secondary x-ray findings may be very valuable in the diagnosis. An intraventricular thrombus may cast a shadow of increased density, calcification within the thrombus or wall of the sac may likewise be noted. In this situation the clot is helpful in the x-ray diagnosis but by interference with the transmission of pulsation another important sign is obscured. Schwedel¹⁷ describes an incisura between the bulge and the remainder of the left ventricular contour just above the diaphragm in the anteroposterior view.

Massive aneurysms involving the entire left ventricular wall are commonly overlooked, since the x-ray appearance is then merely one of an enlarged left ventricle.

Even though the most common site for cardiac aneurysm is the apex, this location does not lend itself to easy recognition by routine x-ray study. Surrounding structures, especially the diaphragm, obscure this area. Special technic, including examination under different phases of respiration and the use of effervescent substances to inflate the stomach, may be attempted to reveal the apical aneurysm protruding into the gas bubble.

Posterior-wall aneurysms, which are less common, have been demonstrated by Schwedel¹⁷ by means of fluoroscopy and repeated radiographic examinations that showed progressive increase in size of the localized bulge. Occasionally, the barium-filled esophagus is displaced by the aneurysm of the posterior wall in the left oblique view.⁹

The aneurysm of the interventricular septum has never been diagnosed clinically to our knowledge. The presence of calcification in the septum, however, may lead to its recognition.

Angiocardiography may be of great help in the diagnosis since this method portrays the cardiac chambers and more clearly elucidates deformities of the cardiac contours. It is obvious that a clot may interfere with the deposition of the radio-opaque substance within the cardiac chamber, and hence the continuity or communication of the deformity of the cardiac shadow with the intraventricular cavity may not be demonstrated and a ventricular aneurysm may be missed.

Differential Diagnosis

Only a few conditions are encountered commonly enough to be considered in the differential diagnosis of cardiac aneurysm. Primary tumors of the heart and pericardium are exceedingly rare.³⁵ Metastatic tumors may be considered when an unusual cardiac bulge is seen in a heart that is not enlarged, and when the bulge pulsates synchronously with the remainder of the heart. Occasionally, the diagnosis may be suspected in patients with

known cancer, or in cases of unexplained heart block.³⁶

Localized pericardial fluid may be differentiated by the history of pericarditis and the nature of the pulsation.

Aneurysms of the descending aorta can usually be distinguished by fluoroscopy and possibly by angiocardiology. A diastolic murmur and a positive serologic test for syphilis will aid in the recognition of an aneurysm of the sinus of Valsalva when it projects to the left.

Diseases associated with pulmonary hypertension may enlarge the conus arteriosus so that it simulates cardiac aneurysm. Carefully performed fluoroscopy will demonstrate that the area involved consists of the entire pulmonary conus rather than a localized ventricular bulge, and the type of cardiac murmur (in cases of mitral stenosis), the presence of congenital heart disease or signs of pulmonary disease aid in this differentiation.

Extracardiac lesions that produce apparent deformities of the cardiac silhouette and may be confused with a cardiac aneurysm are tumors of the mediastinum or lung. Of these, dermoids occur at a younger age and are usually asymptomatic except for pressure symptoms, and there is no antecedent history of myocardial infarction. Sometimes the tumors contain teeth or other bony structures, which are seen on x-ray examination. Teratomas of the mediastinum may distort the cardiac configuration³⁷ but may be associated with teratomas elsewhere, as in the ovary or testis.

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A diverticulum of the pericardium projects to the right in contrast to the usual left-sided cardiac aneurysm. Hydatid cyst of the pericardium can be differentiated by appropriate skin and serologic tests. The para-apical fat triangle is easily differentiated by x-ray examination.

Clinical Course

The presence of a cardiac aneurysm does not in itself affect the clinical course. The underlying cardiac disease, rather than the existence of the aneurysm, determines the development of anginal pains, signs or symptoms of congestive heart failure, arrhythmias or even death. Recurrent acute episodes should not be attributed to the cardiac aneurysm but to the progressive coronary-artery and myocardial disease. Fisher³⁹ has recently reported a case of cardiac aneurysm with rupture. In 1944 Beck³⁹ described a case of ventricular aneurysm in which he grafted a segment of fascia lata over the aneurysm in the hope of preventing

blood pressure The blood pressure in Hartley's¹⁰ 2 cases was reported as 110 systolic, 90 diastolic, and 150 systolic, 90 diastolic Penner's⁶ patient had a blood pressure of 140 systolic, 90 diastolic Consideration of this important feature of blood pressure within the normal range led Parkinson, Bedford and Thomson³ to raise the possibility that previous hypertension when associated with ventricular hypertrophy may exert a protective effect in preventing the development of a cardiac aneurysm The thickened muscular wall of the ventricle is less likely to be involved in its entire thickness after coronary thrombosis, whereas the wall of a heart that has not undergone hypertrophy due to hypertension may be more easily involved in greater proportion, leading to the development of a cardiac aneurysm

It must be noted, however, that in 1 of the 3 cases reviewed by Eliaser and Konigsberg²⁹ the patient had hypertension, as did 50 per cent of those in the series of Brams and Gropper¹⁶ The latter authors question the ability of the hypertrophied myocardium, which they consider abnormal muscle, to protect against the formation of cardiac aneurysms

Electrocardiogram

There is no unanimity of opinion about the electrocardiographic pattern in ventricular aneurysm The earliest papers, summarized by Eliaser and Konigsberg²⁹ in 1939, showed that 23.5 per cent of the tracings revealed a downward direction of the major deflection in Lead 1, with inversion of the T wave, whereas the ventricular complex was upright in Lead 3 On the other hand, in Crawford's⁹ analysis of 13 cases, none of the electrocardiograms showed the changes described by the above authors In 35.3 per cent of the cases reported to 1939,²⁹ a left-axis deviation was present, with major deflections directed downward in Lead 2 and Lead 3 with or without low amplitude of the ventricular complex in Lead 1 Some of the remainder showed left-bundle-branch block or equivocal records

Nordenfelt,³⁰ in his electrocardiographic study of 10 cases, showed that when the aneurysm involved the anterior wall the following pattern often persisted: relatively low R or Q wave with negative T wave in Lead 1, deep S wave with upright T wave in Lead 2, deep S wave with upright T wave in Lead 3, and absent or low R wave and deep S wave in Lead 4 In all leads the ST segment was elevated

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It is apparent that there is no electrocardiographic pattern that is definitely characteristic of ventricular aneurysm A low R wave in Lead 1, however, with deep S waves in Leads 2 and 3, is suggestive and, if associated with elevated ST segments in all leads, can be considered helpful Persistence of this pattern for a considerable period is also helpful since regression of the pattern to normal often occurs after uncomplicated infarction The presence of right-axis deviation with a heart obviously enlarged to the left is rare but may occur in patients with ventricular aneurysm This right-axis deviation occurred in 27.3 per cent of the cases reported by Eliaser and Konigsberg²⁹

The variation in the electrocardiographic pattern found in ventricular aneurysm must be due to many other factors besides the presence of the ventricular aneurysm It is obvious that progression of the underlying heart disease and recurrent myocardial infarcts influence the electrocardiogram Other changes may be due to rotation of the heart, or to alterations in the thrombus within the aneurysm⁵

X-ray Observations

The localized bulging of the left ventricular wall just above the apex is the most characteristic radiographic appearance of cardiac aneurysms The x-ray diagnosis of the aneurysm in this site is comparatively easy In the anteroposterior view, the bulge is most commonly seen just above the apex, and by means of fluoroscopy or lateral and oblique films, the portion of the ventricle involved is identified In the oblique view, the cardiac silhouette shows an abrupt shelving of the anterior wall⁹ Sometimes, pulsation can be seen in the aneurysmal area, but most investigators agree that it is not a necessary criterion for the diagnosis¹⁷ When this paradoxical pulsation occurs in the bulge, it is almost pathognomonic The bulge may become adherent to the pericardium, and, during systole, there may be expansion of the aneurysm with sub-

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and deep S waves in Leads 2 and 3 as occurring occasionally in cases of ventricular aneurysm In the most recent paper that we have seen in the literature on the electrocardiographic pattern of ventricular aneurysm, Goldberger and Schwartz³⁴ emphasize the value of the augmented unipolar right-arm lead In 15 cases of ventricular aneurysm in which the standard leads were variable or tended to show the pattern of low R wave in Lead 1 and deep S waves in Leads 2 and 3, the right-arm lead revealed an upward deflection of the QRS complex, regardless of the site of the infarction or rotation of the heart They regard this upward deflection of the QRS complex in the right-arm lead as so important that the diagnosis of ventricular aneurysm should not be made in its absence One of our patients showed this finding (Fig 2), whereas in Case 2 the pattern was atypical (Fig 4)

It is apparent that there is no electrocardiographic pattern that is definitely characteristic of ventricular aneurysm A low R wave in Lead 1, however, with deep S waves in Leads 2 and 3, is suggestive and, if associated with elevated ST segments in all leads, can be considered helpful Persistence of this pattern for a considerable period is also helpful since regression of the pattern to normal often occurs after uncomplicated infarction The presence of right-axis deviation with a heart obviously enlarged to the left is rare but may occur in patients with ventricular aneurysm This right-axis deviation occurred in 27.3 per cent of the cases reported by Eliaser and Konigsberg²⁹

The variation in the electrocardiographic pattern found in ventricular aneurysm must be due to many other factors besides the presence of the ventricular aneurysm It is obvious that progression of the underlying heart disease and recurrent myocardial infarcts influence the electrocardiogram Other changes may be due to rotation of the heart, or to alterations in the thrombus within the aneurysm⁵

X-ray Observations

The localized bulging of the left ventricular wall just above the apex is the most characteristic radiographic appearance of cardiac aneurysms The x-ray diagnosis of the aneurysm in this site is comparatively easy In the anteroposterior view, the bulge is most commonly seen just above the apex, and by means of fluoroscopy or lateral and oblique films, the portion of the ventricle involved is identified In the oblique view, the cardiac silhouette shows an abrupt shelving of the anterior wall⁹ Sometimes, pulsation can be seen in the aneurysmal area, but most investigators agree that it is not a necessary criterion for the diagnosis¹⁷ When this paradoxical pulsation occurs in the bulge, it is almost pathognomonic The bulge may become adherent to the pericardium, and, during systole, there may be expansion of the aneurysm with sub-

sequent involvement of the pleura or diaphragm. This systolic expansion is one of the bases for the diagnosis by roentgenkymography. Absent pulsation in this area is the other.

Secondary x-ray findings may be very valuable in the diagnosis. An intraventricular thrombus may cast a shadow of increased density, calcification within the thrombus or wall of the sac may likewise be noted. In this situation the clot is helpful in the x-ray diagnosis but by interference with the transmission of pulsation another important sign is obscured. Schwedel¹⁷ describes an incisura between the bulge and the remainder of the left ventricular contour just above the diaphragm in the anteroposterior view.

Massive aneurysms involving the entire left ventricular wall are commonly overlooked, since the x-ray appearance is then merely one of an enlarged left ventricle.

Even though the most common site for cardiac aneurysm is the apex, this location does not lend itself to easy recognition by routine x-ray study. Surrounding structures, especially the diaphragm, obscure this area. Special technic, including examination under different phases of respiration and the use of effervescent substances to inflate the stomach, may be attempted to reveal the apical aneurysm protruding into the gas bubble.

Posterior-wall aneurysms, which are less common, have been demonstrated by Schwedel¹⁷ by means of fluoroscopy and repeated radiographic examinations that showed progressive increase in size of the localized bulge. Occasionally, the barium-filled esophagus is displaced by the aneurysm of the posterior wall in the left oblique view.⁹

The aneurysm of the interventricular septum has never been diagnosed clinically to our knowledge. The presence of calcification in the septum, however, may lead to its recognition.

Angiocardiography may be of great help in the diagnosis since this method portrays the cardiac chambers and more clearly elucidates deformities of the cardiac contours. It is obvious that a clot may interfere with the deposition of the radioopaque substance within the cardiac chamber, and hence the continuity or communication of the deformity of the cardiac shadow with the intraventricular cavity may not be demonstrated and a ventricular aneurysm may be missed.

Differential Diagnosis

Only a few conditions are encountered commonly enough to be considered in the differential diagnosis of cardiac aneurysm. Primary tumors of the heart and pericardium are exceedingly rare.²³ Metastatic tumors may be considered when an unusual cardiac bulge is seen in a heart that is not enlarged, and when the bulge pulsates synchronously with the remainder of the heart. Occasionally, the diagnosis may be suspected in patients with

known cancer, or in cases of unexplained heart block.²⁶

Localized pericardial fluid may be differentiated by the history of pericarditis and the nature of the pulsation.

Aneurysms of the descending aorta can usually be distinguished by fluoroscopy and possibly by angiocardiology. A diastolic murmur and a positive serologic test for syphilis will aid in the recognition of an aneurysm of the sinus of Valsalva when it projects to the left.

Diseases associated with pulmonary hypertension may enlarge the conus arteriosus so that it simulates cardiac aneurysm. Carefully performed fluoroscopy will demonstrate that the area involved consists of the entire pulmonary conus rather than a localized ventricular bulge, and the type of cardiac murmur (in cases of mitral stenosis), the presence of congenital heart disease or signs of pulmonary disease aid in this differentiation.

Extracardiac lesions that produce apparent deformities of the cardiac silhouette and may be confused with a cardiac aneurysm are tumors of the mediastinum or lung. Of these, dermoids occur at a younger age and are usually asymptomatic except for pressure symptoms, and there is no antecedent history of myocardial infarction. Sometimes the tumors contain teeth or other bony structures, which are seen on x-ray examination. Teratomas of the mediastinum may distort the cardiac configuration²⁷ but may be associated with teratomas elsewhere, as in the ovary or testis.

Other benign or malignant intrathoracic tumors are less common but may be confusing when in close proximity to the ventricular shadow.²⁸ With the development of the technic of visualization of the cardiac chambers and related structures by the injection of 70 per cent diodrast solution most of these extracardiac lesions can be delineated.

A diverticulum of the pericardium projects to the right in contrast to the usual left-sided cardiac aneurysm. Hydatid cyst of the pericardium can be differentiated by appropriate skin and serologic tests. The para-apical fat triangle is easily differentiated by x-ray examination.

Clinical Course

The presence of a cardiac aneurysm does not in itself affect the clinical course. The underlying cardiac disease, rather than the existence of the aneurysm, determines the development of anginal pains, signs or symptoms of congestive heart failure, arrhythmias or even death. Recurrent acute episodes should not be attributed to the cardiac aneurysm but to the progressive coronary-artery and myocardial disease. Fisher²³ has recently reported a case of cardiac aneurysm with rupture. In 1944 Beck²⁹ described a case of ventricular aneurysm in which he grafted a segment of fascia lata over the aneurysm in the hope of preventing

its rupture. This patient died a few weeks later of a complicating pneumonia. This direction of surgical effort although brilliant seems unwarranted since Levine³⁵ has stated that rupture of the chronic ventricular aneurysm rarely if ever occurs. In the two largest series of cases that we have encountered,^{16, 17} no case of rupture of the cardiac aneurysm took place.

The prognosis of ventricular aneurysm, therefore, depends on the pre-existing coronary-artery disease, and since this may be static or actually improved by the development of collateral circulation there are many reports of longevity^{3, 8} in the literature. In fact, some of these patients have done and are doing manual labor, and many have carried on the normal activities of daily living without untoward incident. The presence of more than one cardiac aneurysm does not seem to alter the prognosis.¹⁶

In some aneurysms thrombosis and fibrosis do not occur, and because of progressive enlargement the wall of the sac becomes thin, its only support being that of the adherent pericardium. It is in this rare type that rupture may take place. Another of the relatively few complications of the aneurysm itself is the development of embolic phenomena. A small portion of the intra-aneurysmal clot may detach itself and result in hemiplegia, gangrene of the feet, or infarcts of the viscera, kidneys or skin.^{3, 10, 20}

DISCUSSION

If one accepts the statement of Parkinson, Bedford and Thomson³ that 1 out of every 11 patients with myocardial infarction will develop cardiac aneurysm and the autopsy figures of the Massachusetts General Hospital²⁴ showing a 10 per cent incidence of cardiac aneurysm in patients after myocardial infarction, it appears that many cases are being missed clinically. Sigler and Schneider³¹ state that only 0.5 per cent have been diagnosed during life and support our impression that the diagnosis should be made more frequently. It might be well, therefore, to review the important diagnostic features of cardiac aneurysm.

A history of previous infarction can usually be elicited although silent myocardial infarction must be kept in mind.

The presence of abnormal pulsations within the area of cardiac dullness but separate and distinct from the apical impulse may be seen.

A poor, dull first sound despite the increased pulsations may be present.

A localized bulge sometimes accompanied by increased density, calcification, pericardial adhesion or incisura (Schwedel)³ may be demonstrated.

There are also a number of findings that are not in themselves as definitive as those listed above, but their presence should lead to the awareness of the possibility that a ventricular aneurysm exists: an enlarged heart with distant heart sounds, an enlarged heart with the physical finding of normal

blood pressure³, an enlarged heart with the electrocardiographic finding of right-axis deviation or the finding of an upward deflection of the QRS complexes in the right-arm lead³⁴, and the late occurrence of cerebral or other embolism in a patient who has had a myocardial infarction.³

In view of the recent emphasis on early ambulation after myocardial infarction, a warning note about the pathogenesis of cardiac aneurysm must be sounded. It has frequently been pointed out^{10, 14, 16, 40} that many patients who have developed ventricular aneurysms have received inadequate bed rest after the acute episode of infarction. Zimdahl and Busuego⁴⁰ considered it significant in the development of the aneurysm in one of their patients that he was sent back and forth to a diagnostic laboratory for three days after his attack. Some patients may have had the silent type of myocardial infarction, and no bed rest at all was prescribed. During the period of myomalacia every precaution must be taken to support the weakened myocardium, and undoubtedly bed rest reduces the work of the heart and allows a firmer scar to develop.

It will be interesting to note the effect on the incidence of rupture of ventricular aneurysm of the introduction in 1945⁴¹ of anticoagulant therapy for myocardial infarction. Reduction of clot formation within the aneurysm theoretically may result in a thin-walled sac that does not have the support of a firm, lamellated clot. The x-ray diagnosis may be more difficult because of the lack of increased density and calcification in the bulge. This type, having only the pericardium as its support, tends to increase its size and is more likely to rupture. On the other hand, the late embolic manifestations mentioned above may be prevented.

SUMMARY

Two cases of ventricular aneurysm diagnosed during life are reported. The patients are not incapacitated by their cardiac aneurysms, and their cardiac symptoms are referable to the underlying cardiac disease.

The increased incidence, physical and x-ray findings, and clinical course of cardiac aneurysm are reviewed. Certain criteria for the ante-mortem diagnosis, as well as the brighter outlook regarding prognosis and longevity, are stressed.

The effect on cardiac aneurysms of two recently introduced regimens in the therapy of myocardial infarction — early ambulation and anticoagulant therapy — are briefly discussed.

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OSTEITIS PUBIS*

M ABRAMS, M D,* I SEDLEZKY, M D,† AND DAVID B STEARNS, M D‡

BOSTON

THE number of reported cases of osteitis pubis following suprapubic or retropubic prostatectomy¹⁻¹¹ suggests that it is a rare complication. Since this is not in accord with our own experience we herewith present 5 cases with observations relating to diagnosis and treatment. Two of them followed retropubic prostatectomy, and 2 followed suprapubic prostatectomy, the fifth case followed an abdominoperineal resection for carcinoma of the rectum.

CASE REPORTS

CASE 1 J W, a 61-year-old man, was admitted to the hospital with the chief complaint of frequency of urination during the day and night and hesitancy and diminution in the force of the urinary stream. An examination of the urine revealed 15 to 20 white cells and 3 to 5 red cells per high-power field. Urine culture grew out many colonies of hemolytic *Staphylococcus aureus*. The findings of the lower urinary tract were consistent with an obstructing prostate. Three days later a retropubic prostatectomy was done. The postoperative course was uneventful.

Thirty-eight days after the operation the patient first began to notice pain over the symphysis pubis. The pain gradually became worse, and 12 days thereafter he was readmitted to the hospital. Coughing, walking or motion of the legs in any direction increased the severity of the pain. Except for marked tenderness over the symphysis pubis, physical examination was entirely negative.

The white-cell count was 15,000, the blood acid and alkaline phosphatase as well as the phosphorus, were normal. Urine culture showed a few colonies of *Pseudomonas aeruginosa* and *Staph. albus*. A roentgenogram taken the day after admission showed some irregularity and erosion of the upper edges of the inner margins of the pubic bones. Successive films demonstrated progressive destruction of the medial margins of the pubic bones. Healing was demonstrated by the laying down of dense bone at the articular margins of the pubis.

Streptomycin, penicillin sulfadiazine and sulfamerazine failed to alter the clinical course of the disease. Diathermy and local heat were ineffective. Opiates were necessary to control the pain and discomfort. At the end of 3 weeks, an orthopedic belt which had only aggravated the symptoms in the acute phase of the disease, now gave definite relief. Improvement occurred slowly. The patient was free of all pain 9 weeks after the onset of symptoms.

CASE 2 M H, a 74-year-old man, was admitted to the hospital in acute urinary retention. For 1 year prior to admission he had complained of nocturia three to five times and of difficulty in starting the urinary stream. The prostate on rectal examination was very large. Examination of the urine revealed 3 to 5 white cells per high-power field. Culture of

*Assistant in genitourinary surgery Harvard Medical School resident in urology Beth Israel Hospital.

†Resident in radiology Beth Israel Hospital.

‡Assistant professor of urology Boston University School of Medicine visiting urologist, Massachusetts Memorial Hospitals associate visiting urologist, Beth Israel Hospital.

the urine grew out a few colonies of *Ps aeruginosa*. Five days later a retropubic prostatectomy was done. The post-operative course was uneventful. A urine culture taken the day the catheter was removed grew out many colonies of *Aerobacter aerogenes* and *Ps aeruginosa*.

Twenty-nine days after operation the patient began to complain of a constant dull pain over the symphysis pubis and along the inner aspects of both thighs. Coughing, walking or sitting aggravated the pain. There was definite localized tenderness over the symphysis pubis. On examination the white-cell count was 12,000, the acid and alkaline phosphatase levels were normal. A culture of the urine grew out *Ps aeruginosa*. A roentgenogram of the pelvis taken 7 days after the onset of symptoms revealed slight erosion of the

tional surgical procedure was necessary. Four months after operation the patient first began to complain of a dull aching pain in both groins. The pain was referred to the perineum and along the inner aspects of both thighs. Gradually these symptoms became worse, and 2 months thereafter the discomfort required hospitalization.

Physical examination revealed an elderly man in obvious pain. Coughing, sitting or any movement of the lower extremities increased the severity of the symptoms. There was definite tenderness over the symphysis pubis. On examination the urine contained 15 to 20 white cells and 5 to 10 red cells per high-power field. Culture of the urine showed many colonies of *Ps aeruginosa*, as well as a moderate number of *Escherichia coli*. The blood calcium, acid phosphatase, al-

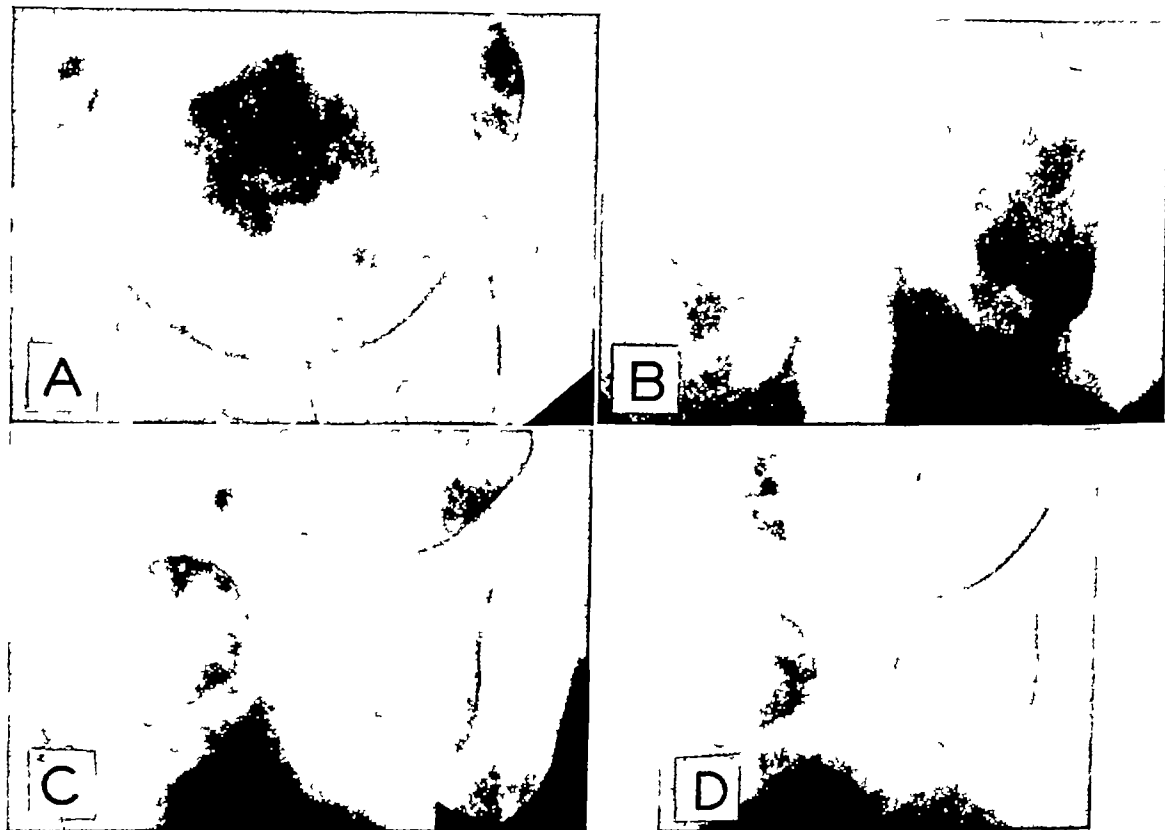


FIGURE 1 Roentgenograms in Case 3

A = preoperative film, showing normal symphysis pubis (note prostatic calculi). B and C = films taken six months after suprapubic prostatectomy, with the patient standing first on the left foot and then on the right (note the wide symphysis and considerable mobility of the pubic bones). D = film taken eighteen months after operation, showing the symphysis pubis to be irregularly widened (the bony margins are dense, and the adjacent bone sclerotic, the process is apparently healed).

right os pubis. Another roentgenogram taken 1 month later demonstrated further destruction of the upper medial corner of the left os pubis. Penicillin, streptomycin and sulfadiazine had no effect on the clinical course of the disease. Large doses of vitamin B given intravenously in conjunction with a course of deep x-ray therapy proved ineffective. An orthopedic belt, which extended from above the crest of the ilium to below the symphysis pubis, allowed the patient to become ambulatory 2 weeks after the onset of symptoms. Six weeks later he was entirely free of pain.

CASE 3 F W, a 66-year-old man, had a two-stage suprapubic prostatectomy for a benign prostatic hypertrophy. Numerous calculi were present within the prostate. After the second stage, the immediate postoperative course was complicated by the development of epididymitis. The elevated temperature returned to normal in 6 days, and no addi-

kaline phosphatase and phosphorus were normal. A roentgenogram of the pelvis demonstrated the wide symphysis pubis that is consistent with osteitis pubis. Films taken with the patient standing first on the left foot and then the right foot revealed the extreme mobility of the pubic bones at this time (Fig 1B and C). Immobilization of the pubis with a tight orthopedic belt gave the patient some relief. Eight days later he was ambulatory with the aid of a cane. Twenty days later he was discharged, very much improved, but still unable to walk without the aid of the tight belt and cane. A roentgenogram taken 1 year later showed an irregularly widened symphysis pubis. The bony margins were dense, and the adjacent bone sclerotic. This represented a healed process (Fig 1D).

CASE 4 A M, a 71-year-old man, had a two-stage suprapubic prostatectomy for a benign hypertrophy of the prostate

in another hospital. He was discharged 25 days after the second operation with a small, draining suprapubic sinus. Urinary control was excellent. Seventy-seven days after operation he was admitted for the first time to the Massachusetts Memorial Hospitals because of severe pain over the symphysis pubis and across the inner aspects of both thighs. Coughing, walking or motion of the legs in any direction aggravated the pain. These symptoms had begun 3 weeks earlier and had gradually become worse. There was tenderness on pressure over the symphysis pubis. A slight purulent discharge at the lower angle of the suprapubic wound was noted. The rest of the examination was entirely negative.

On admission, the urine contained many white cells and 2 or 3 red cells per high-power field. Culture of the urine grew out *Ps aeruginosa* and *Esch coli*. The white-cell count was 15,500. The acid and alkaline phosphatase determinations were normal. A roentgenogram of the pelvis showed a wide symphysis pubis with irregular erosion of the bone surfaces (Fig 2). A diagnosis of osteitis pubis was made. Two days



FIGURE 2 Roentgenogram Taken in Case 4 Seventy-Seven Days after a Suprapubic Prostatectomy. Note the unusually wide symphysis, with irregular erosion of the bony surfaces, the pubic bones show patchy rarefaction.

later a course of deep x-ray therapy was given. The patient received 200 r daily for 6 days over the pubis. Large doses of components of the vitamin B complex were also given. On the 4th day of therapy, definite improvement was noted. Four days later, the patient was able to move with only moderate discomfort. Seven days later he was discharged totally free from symptoms. The sinus at the lower end of the incision was healed. (No antibiotics or sulfonamides were given to this patient.)

CASE 5* E S, a 50-year-old man, was admitted to the Massachusetts Memorial Hospitals for an abdominoperineal resection for an adenocarcinoma of the rectum. He had a moderately febrile postoperative course. Two months thereafter he was readmitted to the hospital because of constant pain over the symphysis pubis. Standing, sitting, coughing or walking increased the severity of the pain. On admission the temperature was 101°F. Examination of the urine showed 5 to 6 white cells per high-power field. Urine culture grew out many colonies of *Ps aeruginosa* and hemolytic *Staph aureus*. The white-cell count was 12,000. Physical examination revealed a functioning colostomy, a small draining sinus at the lower end of the abdominal incision and tenderness to even slight palpation over the symphysis pubis. Cultures from the draining sinus grew out *Ps aeruginosa*. A roent-

genogram of the pelvis demonstrated beginning erosion of the medial surfaces of both pubic bones with widening of the symphysis.

Penicillin and sulfadiazine were started on admission. Four days later the temperature returned to normal. However, the pain over the symphysis pubis persisted for 3 weeks, when gradually it began to subside. Four weeks later the patient was free of all pain. A roentgenogram taken 7 months after the operation again demonstrated a wide symphysis pubis. Healing was clearly represented by the irregular, dense and sclerotic medial margins of the pubis.

DISCUSSION

Although the etiology of this condition remains obscure, the symptoms, physical findings, laboratory data and course are all suggestive of an inflammatory process. Wheeler,⁵ on the basis of his experimental studies, did not consider osteitis pubis as an inflammatory process. He attempted to reproduce this disease in the rabbit by introducing urine, both sterile and infected, under the periosteum of the pubis. This failed to produce any evidence of periostitis. The introduction of foreign bodies under the periosteum and even deliberate trauma to the space of Retzius failed to reproduce periostitis or osteitis. Wheeler therefore preferred to consider this syndrome as an example of acute bone atrophy of the Sudeck type. Sudeck's acute bone atrophy has been described¹² as a post-traumatic type of lesion that usually occurs in the neighborhood of multiarticular joints such as the wrist and foot and is regarded as a neurovascular disturbance. In addition to pain over the involved joint there is swelling, atrophy of the subcutaneous tissues and trophic changes in the skin. Roentgenologically, there is very marked decalcification of the bones.

We believe that osteitis pubis is of an inflammatory nature. The urine that escapes into the space of Retzius during and after operation slowly saturates and puddles in the retropubic soft tissues and sets up an inflammatory process that progresses so that the bone eventually becomes involved. At this point the clinical symptoms become evident. Although no bone biopsies were taken in any of the cases reported above, Muschat⁷ reports a curettage biopsy of the symphysis pubis in a patient suffering from osteitis pubis. The specimen showed inflammation. Chemotherapy failed to alter the clinical course of the disease in any of our cases. Trauma to the symphysis pubis — by retractors, drains or needle puncture — may be a factor in the development of this clinical entity. The fact that osteitis pubis occurs so infrequently in women after extensive gynecologic operations suggests that trauma alone is not the sole cause.

The diagnosis of osteitis pubis offers no particular problem clinically. A history of a recent prostate operation and the development of localized pain over the symphysis should immediately suggest this condition. The pain, which is at first mild, soon becomes severe and radiates to the perineum and over the inner aspects of the thighs. Any motion

*Permission to cite this case was obtained from Dr. C. Howe.

of the lower extremities increases the intensity of the pain. The pain is probably the result of muscle pull on the inflamed periosteum, in addition to increased intraosseous tension. In the 5 cases reported above, pain over the symphysis pubis appeared as early as twenty-nine days (Case 2), and as late as a hundred and twenty days after operation (Case 3). Some authors report these symptoms as early as fourteen days after the operation. Physical findings are usually entirely negative except for the localized tenderness over the symphysis pubis. A suprapubic sinus is occasionally found (Cases 4 and 5). During the early stages of the disease the patient usually has a mild fever. A white-cell count of 12,000 to 15,000 was present in all our cases. A moderate anemia was noted in Cases 4 and 5. The blood calcium, phosphorus, acid and alkaline phosphatase were normal. Examination of the urine revealed many white cells. Cultures of the urine grew out *Ps. aeruginosa*, *Esch. coli* and hemolytic *Staph. aureus*. *Ps. aeruginosa* was predominant and present in all cases.

Though this condition can be suspected on the basis of the clinical features, the final diagnosis rests on the roentgenologic findings. The technic of x-ray examination is important. The use of a fine-focus tube, a small cone and a Bucky diaphragm with the patient in the prone position are all essential factors in demonstrating the earliest bony changes. Stereoscopic films may be of help. The rectum should be free of gas and feces.

In general, roentgenographic changes have been observed two or three weeks after the onset of symptoms. However, in 1 case (Case 2) changes were noted as early as seven days. The earliest changes consist of blurring of the symphyseal contours of the pubis, with patchy osteoporosis of the contiguous bone. As the process continues bilateral, irregular and progressive destruction of the opposing articular surfaces of the symphysis pubis occurs. This is largely symmetrical, but one side may be more involved. No sequestra are produced or expected since the bone involved is predominantly spongy. It is a fact that necrotic, spongy bone is removed by resorption, and only compact bone by sequestration.¹³ The progressive widening of the symphysis pubis is predominantly the result of loss of bone substance rather than just a separation of the pubic bones. The changes in the symphysis pubis are sufficient to permit considerable vertical mobility of the pubic bones. To show this, films were taken with the patient standing first on one foot and then on the other (Fig 1B and C).

The healing period is variable, depending upon the extent of the lesion. Most authors agree that this period varies from two to six months. Roentgenologically, healing is signalled by the arrest in the progress of the bone destruction and the laying down of dense bone at the margins of the eroded symphysis pubis. Cases have been described in

which the end result is ankylosis of the symphysis pubis.

The differential diagnosis included a simple pre-vesical-space infection without bone involvement, acute and chronic hematogenous osteomyelitis of the pubic bone, a metastatic lesion from the prostate and primary bone sarcoma.

A simple infection of the space of Retzius without bone involvement should offer no problem in the differential diagnosis. The clinical course is mild, and roentgenologic changes are absent. An acute hematogenous pyogenic osteomyelitis will give a more severe, more acute systemic reaction as well as more pronounced local changes. A specific chronic infection such as tuberculosis can be less easily ruled out purely on the basis of the initial roentgenographic changes. Tuberculosis of the symphysis pubis is extremely rare. The initial destructive phase may be difficult to distinguish from a metastatic lesion from a prostatic carcinoma. The characteristic restricted localization of bone resorption to the pubis, the history of a recent prostatic operation, the low-grade febrile course and the prominence of osteolysis with little or no osteoblastic features are against a metastatic lesion from the prostate. The acid and alkaline phosphatase was normal in the 5 cases of osteitis pubis reported above. The lack of periosteal reaction and the absence of spiculation or tumor mass are all against a diagnosis of primary bone sarcoma.

There is no specific treatment for this clinical entity. In the acute phase the intense suprapubic pain forces the patient to complete bed rest. Opiates and sedatives are necessary to keep the patient comfortable. In our cases, the use of penicillin, streptomycin and sulfadiazine did not in any way alter the course of the disease. Diathermy and local heat over the symphysis had little effect. The injection of 1 per cent novocain into the painful spastic muscles of the upper thigh occasionally gave temporary relief. In 1 case the use of deep x-ray therapy appeared to be beneficial. In 2 other cases in which it was tried it was of no benefit. Large doses of components of the vitamin B complex were also ineffective. After the subsidence of the acute process, which lasted between eighteen and twenty-one days, an orthopedic belt, extending from above the crest of the ilium to below the symphysis pubis, immobilized the symphysis pubis and proved beneficial. This belt, with the aid of a cane, allowed early motion. Relief of symptoms occurred slowly.*

SUMMARY

Five cases of osteitis pubis are reported. Two of them followed retropubic prostatectomy, 2 followed suprapubic prostatectomy, and the fifth an abdominoperineal resection for carcinoma of the rectum. We do not know the specific etiology of

*Since this paper was submitted for publication 4 additional cases of osteitis pubis have been reported: 2 after retropubic surgery and 2 after transurethral resection.¹⁴

osteitis pubis but consider it to be inflammatory. Trauma to the symphysis pubis, by retractors, drains or needle puncture, may be a factor in the development of this clinical entity. The fact that osteitis pubis occurs so infrequently in women after extensive gynecologic operations suggests that trauma alone is not the sole cause.

The diagnosis of osteitis pubis offers no particular problem. A history of a recent prostatic operation and the development of localized pain over the symphysis pubis should immediately suggest this entity. The roentgenologic findings are typical and definitely establish the diagnosis. The medial articular aspects of the pubic bones are predominantly involved. First there is merely blurring of the bony contours associated with osteoporosis of the adjacent bone. Then, there is slow, progressive erosion of the symphyseal aspects of the pubic bones. Healing is shown by arrest in the progress of the bone destruction and the laying down of dense sclerotic bone at the margins of the widened symphysis pubis. Urine cultures in the 5 cases reported grew out *Pseudomonas aeruginosa*. The significance of this finding is not established.

There is no specific treatment of osteitis pubis. Although deep x-ray therapy and large doses of com-

ponents of the vitamin B complex appeared to help 1 patient, they proved of no help in 2 other cases. Penicillin, streptomycin, sulfadiazine and sulfathiazole were ineffective in controlling any of the symptoms. The disease, though distressing and of long duration, is self limited and does not require surgical intervention.

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WERNER'S SYNDROME*

A Report of Two Cases

JACOB SCHOTT, M.D.,† AND SIDNEY DANN, M.D.‡

BROOKLYN, NEW YORK

OCCASIONALLY the opportunity of seeing one of the rarer disease states or syndromes presents itself to most physicians. Their recognition can be made more readily possible if those who see them bring them to the attention of the profession.

Our purpose in this paper is to add 2 more cases of Werner's syndrome to the literature, to review briefly the more pertinent features of the syndrome and to outline the criteria in as simple a manner as possible, so that they can be easily remembered. Thannhauser,§ in 1945, added 5 cases to the literature and in a most excellent article summarized all that had been published on the subject.

ETIOLOGY

The etiology of the disease is not definitely known. The accepted theory at present is that it is due to a defect in the germ plasma that becomes evident in

the third or fourth decade of life. That it is a primary endocrine disturbance has been excluded. Although there is not much doubt that an endocrine element is present, this is thought to be secondary and not primary.

Heredity plays a role, there is frequently collateral occurrence in brothers and sisters of one generation.

DIAGNOSIS

Usually the first frank manifestation of the syndrome is premature graying of the hair, soon followed by thinning.

The shortness of stature dates back to the adolescent age. Birth and childhood development are normal, but in the adolescent years these patients do not maintain the expected growth increase.

Not long after the graying of the hair, which usually starts about the age of twenty, the extremities, particularly the lower ones, begin to take on a spindly appearance. Much discussion and investigation of the skin changes has resulted in the conclusion that they are not sclerodermatous in character. From the waxy, taut, atrophic appearance, at first glance one is apt to mistake them for sclero-

*From the Medical Service, Cumberland Hospital (Service of Dr. James Tesler, Dr. J. J. Guttman, director of medicine).

†Associate in medicine, Cumberland Hospital.

‡Assistant in medicine, Cumberland Hospital.

§Thannhauser S. J. Werner's syndrome (progeria of adults) and Rothmund's syndrome: two types of closely related hereditary atrophic dermatoses with juvenile cataracts and endocrine features: critical study with five new cases. *Ann. Int. Med.* 23:559-626, 1945

of the lower extremities increases the intensity of the pain. The pain is probably the result of muscle pull on the inflamed periosteum, in addition to increased intraosseous tension. In the 5 cases reported above, pain over the symphysis pubis appeared as early as twenty-nine days (Case 2), and as late as a hundred and twenty days after operation (Case 3). Some authors report these symptoms as early as fourteen days after the operation. Physical findings are usually entirely negative except for the localized tenderness over the symphysis pubis. A suprapubic sinus is occasionally found (Cases 4 and 5). During the early stages of the disease the patient usually has a mild fever. A white-cell count of 12,000 to 15,000 was present in all our cases. A moderate anemia was noted in Cases 4 and 5. The blood calcium, phosphorus, acid and alkaline phosphatase were normal. Examination of the urine revealed many white cells. Cultures of the urine grew out *Ps aeruginosa*, *Esch coli* and hemolytic *Staph aureus*. *Ps aeruginosa* was predominant and present in all cases.

Though this condition can be suspected on the basis of the clinical features, the final diagnosis rests on the roentgenologic findings. The technic of x-ray examination is important. The use of a fine-focus tube, a small cone and a Bucky diaphragm with the patient in the prone position are all essential factors in demonstrating the earliest bony changes. Stereoscopic films may be of help. The rectum should be free of gas and feces.

In general, roentgenographic changes have been observed two or three weeks after the onset of symptoms. However, in 1 case (Case 2) changes were noted as early as seven days. The earliest changes consist of blurring of the symphyseal contours of the pubis, with patchy osteoporosis of the contiguous bone. As the process continues bilateral, irregular and progressive destruction of the opposing articular surfaces of the symphysis pubis occurs. This is largely symmetrical, but one side may be more involved. No sequestra are produced or expected since the bone involved is predominantly spongy. It is a fact that necrotic, spongy bone is removed by resorption, and only compact bone by sequestration.¹³ The progressive widening of the symphysis pubis is predominantly the result of loss of bone substance rather than just a separation of the pubic bones. The changes in the symphysis pubis are sufficient to permit considerable vertical mobility of the pubic bones. To show this, films were taken with the patient standing first on one foot and then on the other (Fig 1B and C).

The healing period is variable, depending upon the extent of the lesion. Most authors agree that this period varies from two to six months. Roentgenologically, healing is signalled by the arrest in the progress of the bone destruction and the laying down of dense bone at the margins of the eroded symphysis pubis. Cases have been described in

which the end result is ankylosis of the symphysis pubis.

The differential diagnosis included a simple pre-vesical-space infection without bone involvement, acute and chronic hematogenous osteomyelitis of the pubic bone, a metastatic lesion from the prostate and primary bone sarcoma.

A simple infection of the space of Retzius without bone involvement should offer no problem in the differential diagnosis. The clinical course is mild, and roentgenologic changes are absent. An acute hematogenous pyogenic osteomyelitis will give a more severe, more acute systemic reaction as well as more pronounced local changes. A specific chronic infection such as tuberculosis can be less easily ruled out purely on the basis of the initial roentgenographic changes. Tuberculosis of the symphysis pubis is extremely rare. The initial destructive phase may be difficult to distinguish from a metastatic lesion from a prostatic carcinoma. The characteristic restricted localization of bone resorption to the pubis, the history of a recent prostatic operation, the low-grade febrile course and the prominence of osteolysis with little or no osteoblastic features are against a metastatic lesion from the prostate. The acid and alkaline phosphatase was normal in the 5 cases of osteitis pubis reported above. The lack of periosteal reaction and the absence of spiculation or tumor mass are all against a diagnosis of primary bone sarcoma.

There is no specific treatment for this clinical entity. In the acute phase the intense suprapubic pain forces the patient to complete bed rest. Opiates and sedatives are necessary to keep the patient comfortable. In our cases, the use of penicillin, streptomycin and sulfadiazine did not in any way alter the course of the disease. Diathermy and local heat over the symphysis had little effect. The injection of 1 per cent novocain into the painful spastic muscles of the upper thigh occasionally gave temporary relief. In 1 case the use of deep x-ray therapy appeared to be beneficial. In 2 other cases in which it was tried it was of no benefit. Large doses of components of the vitamin B complex were also ineffective. After the subsidence of the acute process, which lasted between eighteen and twenty-one days, an orthopedic belt, extending from above the crest of the ilium to below the symphysis pubis, immobilized the symphysis pubis and proved beneficial. This belt, with the aid of a cane, allowed early motion. Relief of symptoms occurred slowly.*

SUMMARY

Five cases of osteitis pubis are reported. Two of them followed retropubic prostatectomy, 2 followed suprapubic prostatectomy, and the fifth an abdominoperineal resection for carcinoma of the rectum. We do not know the specific etiology of

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was completely normal. Three other siblings had died at birth, a fourth had died at the age of 2 weeks.

The patient weighed 102 pounds and was 4 feet, 10 inches in height. Her habitus was strikingly characteristic—spindly arms and legs, with a normally developed trunk. She had the typical bird-like facies resulting from a receding chin, tendency to beaking of the nose and the wearing of powerful lenses in her eyeglasses. Her gait was unsteady because of the atrophy of the muscles of the lower extremities and the high plantar arch, but she walked without any characteristic aberration. Her hair was diffusely sparse and was dyed black. She was of average intelligence and of rather cheerful disposition. No respiratory distress or asthenia was noted.

The right eye showed a buphthalmos (post-glaucoma), and the left a surgical coloboma. Some fibrosis of the lens bed was noted. The fundus seen through a +15 lens was slightly paler than normal, the vessels were moderately sclerotic, but there were no hemorrhages, exudates or pigmentation. The movements of the extraocular muscles were normal. There was mild circumcorneal injection of the left eye. The teeth were in good condition. The tongue was moist, with well developed papillae. The pharynx was clear. The ears were normal and did not project from the sides of the head in any unusual fashion. The eardrums were also normal. The eyelashes and eyelids were sparse. The voice appeared to be weak and somewhat high pitched (confirmed by the patient's statement), but indirect laryngoscopy did not reveal the hyperemic or keratotic changes described in this condition. The neck was supple. There was no distention of the veins, no tracheal deviation and no palpable thyroid gland.

The lungs were clear to percussion and auscultation. The heart was not enlarged, and the sounds were of fair quality. The aortic second sound was louder than the pulmonic. There was a Grade III, blowing systolic murmur over the entire precordium, maximal over the base, there were no thrills. Sinus rhythm was normal.

The left breast showed normal development, no masses or tenderness was noted. On the right side there was a healed mastectomy scar with no evidence of infiltration or tenderness in this region.

The abdomen was moderately obese and flabby. There was slight tenderness in the right upper quadrant, but no palpable masses or viscera.

Neurologic examination was entirely normal.

There was marked atrophy of the musculature of all the extremities, most pronounced in the distal segments, and this was accompanied by a moderate degree of weakness. The skin also appeared to be atrophic and over some of the terminal phalanges appeared to be tightly bound down to the underlying tissues, although true scleroderma was not present. Owing to the muscular atrophy the bony prominences of the fingers and toes were more prominent. The instep was markedly arched, and the patient used metal arches in her bathroom slippers for ambulation. There was bilateral hallux valgus. Callosities, the size of a 25-cent piece, were noted in the skin over the heads of the first and fifth metatarsals and over the calcaneus, these areas were not tender. On the right medial and the left lateral malleoli there were ulcerations about the size of a dime. These were excavations bordered by corn-like areas similar to those described above. The bases were greyish yellow, and there was no discharge. The areas were quite tender to the touch. Three scabrous callosities were also noted over the lower tibial areas. The tip of the third right toe was reddened, but no discharge was noted. There was no clubbing or edema. There were good pulsations of the posterior tibial and dorsalis pedis vessels.

The skin was dry and atrophic, with a moderate degree of fine scaling. There were no telangiectases, petechiae or jaundice. The nails were well developed but showed evidence of having been bitten. No fat pads were noted. There was a normal distribution of the female hair.

Rectal examination was negative.

Pelvic examination showed a parous introitus. There were no abnormal findings.

The temperature was 98.6°F, the pulse 80, and the respirations 20. The blood pressure was 110/70.

Examination of the blood revealed a red-cell count of 2,500,000, with a hemoglobin of 10 gm per 100 cc., and a white-cell count of 12,900, with 40 per cent neutrophils and

60 per cent lymphocytes. The sedimentation rate (Linzenmeier method) was 18 mm in 43 minutes. The urine, which had a specific gravity of 1.010, gave a negative to +++ test for sugar, a negative test for albumin and a negative test for acetone, the sediment contained an occasional white cell. The blood sugar was 103 to 225 mg, the urea nitrogen 15 mg, the calcium 9.5 to 11.0 mg, the phosphorus 3.0 to 6.5 mg, the uric acid 3.4 mg, the creatinine 1.6 mg, and the cholesterol 200 mg per 100 cc., with 25 per cent cholesterol esters. The total protein was 6.8 gm per 100 cc., with 4.7 gm of albumin and 2.1 gm of globulin, and the carbon dioxide combining power 56 to 68 vol per cent. The urea clearance was 32 per cent. The phenolsulfonephthalein test showed 45 per cent excretion of the dye in 2 hours. The galactose tolerance test showed the excretion of 3.2 gm in the urine. The alkaline phosphatase was 1.6 Bodansky units per 100 cc. The cephalin flocculation and Mazzini tests were negative. The basal metabolic rate was +1 per cent.

Oscillometric findings on the left were 2.5 at the wrist, 2 above the ankle, 4 below the knee and 4 above the knee, and on the right, 1.5 at the wrist, 4 above the ankle, 4 below the knee and 4 above the knee.

Electrocardiograms, which revealed a tendency to left-axis deviation (with a small Q wave and isoelectric T wave in Lead 3, inverted T wave in Lead CF₂ and upright but low-voltage T wave in Lead CF₄), were interpreted as showing questionable myocardial damage.

X-ray examination of the chest was negative except for evidence of removal of the right breast. Films of the feet demonstrated marked hallux valgus on the right and a moderate degree on the left. There were no apparent gross abnormalities in the bones of the upper and lower extremities. The hands disclosed normal bone texture and density. Films of the skull showed hyperostosis of the frontal and parietal bones bilaterally. The pituitary fossa was small but within normal limits. There was no evidence of increased intracranial pressure or bone erosion.

The patient was placed on partial bed rest and given 200 gm of carbohydrate, 75 gm of protein and 40 gm of fat. She was fairly well regulated on 15 units of protamine zinc insulin and 15 units of regular insulin given in separate syringes in the morning. She also received the following medications three times daily: nicotinic acid, 200 mg, vitamin C, 200 mg, and vitamin B₁, 20 mg. Papaverine, which had been given in doses of 0.1 gm (1½ gr) three times daily, was discontinued because of nausea. The patient claimed considerable subjective improvement on this medication, she stated that her legs felt "looser and stronger." The ulcerations healed slowly, leaving thin scabrous lesions. Of course, it is not possible to determine the relative roles played by the bed rest and the medications in the healing of these long-standing lesions. She was placed gradually on an ambulatory status and discharged as "improved" after 7 weeks in the hospital.

CASE 2. M.B., a 45-year-old woman, the sister of the patient in Case 1, was admitted to the Cumberland Hospital on February 10, 1948, complaining of chest pain of 2 days' duration. The pain was described as precordial and substernal and continuous in severity, with no radiation. She complained of weakness and had noted dyspnea only on talking. There was no cough, edema or palpitations and no previous similar episodes.

The past history included diabetes of 16 years' duration, the diagnosis had first been made during routine urine examination while the patient was undergoing treatment for a foot infection. The disease had been fairly well controlled on 10 units of regular insulin and 10 units of protamine zinc insulin taken in separate syringes in the morning. Three and a half years prior to admission a cataract developed in the right eye, and this was removed 6 months later. One year before admission a cataract extraction was done on the left eye. Vision had been poor. Glaucoma developed in the right eye postoperatively. The patient had had gray hair since the age of 40. Three years prior to admission ulcers on the legs entirely similar to those described in Case 1, as well as corns over the bony prominences on the soles of the feet, developed. The ulcers were painful, and she had great difficulty in walking. She stated that the legs felt very cold and she was bothered by cold weather.

dermatous extremities, but on more careful examination, it is found that the skin can be elevated easily from the subcutaneous structures. It is in the latter structures that the fault lies. The subcutaneous fat tissue is practically absent, and the underlying muscle is extremely thin and atrophic.

Areas of circumscribed hyperkeratoses and ulcerations are not long in appearing, superimposed on the underlying skin changes. That the ulcers are not completely trophic is shown by their readiness in successfully taking a skin graft. The ulcers appear most frequently on areas subjected to pressure—the malleoli of the ankles and over the Achilles tendon, heels and toes. They are due merely to pressure on areas where the skin is tightly drawn over the bone without any protective, subcutaneous fat padding. The hyperkeratotic areas are present chiefly on the soles and over the heels and the heads of the first and fifth metatarsals.

Cataracts fall into the class of juvenile cataracts. Werner, as a student on the ophthalmology wards, first described the occurrence of juvenile cataracts with scleroderma. Star-like opacities develop, mostly on the posterior pole and on the periphery of the lens.

Diabetes may be present in the overt or latent states. There may be only a tendency to this disorder of metabolism as evidenced by abnormal glucose tolerance curves, or the disease may be full blown. Both cases reported below were in diabetic patients, and one, particularly, is rather difficult to control with the usual measures.

Generalized arteriosclerosis is another manifestation of Werner's syndrome. It is the usual type of arteriosclerosis and may result in early complications involving the circulatory system.

Underdevelopment of the sexual organs is a constant finding. Most of the female patients menstruate for some time at least, whereas in the males, erections and the ability to have intercourse are also preserved for a period.

Osteoporosis can readily be demonstrated in roentgen-ray studies of the bones. It has been found, too, in some cases that areas of metastatic calcification exist.

THERAPY

In view of the abiotrophic nature of the disease, one cannot hope to accomplish a great deal along curative lines. However, a certain degree of symptomatic improvement can be obtained. The diabetes can be controlled by the usual methods. Generally, the diabetic state in these patients is not too severe, although occasionally they present problems in control. Thyroid should be given for the usual indications of a hypothyroid state. The cataracts may require iridectomy as in the cases reported below. For the skin changes we have been using large doses of components of the vitamin B complex, especially nicotinic acid, with satisfactory results. Some of the

tautness of the skin and the immobility of the ankles has been relieved, and the patients have expressed considerable subjective relief. The smaller ulcerations have healed. Larger skin ulcerations are said to respond to grafting.

Finally, in view of the hypogonadism, negative calcium balance, diabetes and increased urinary gonadotropins, it has been suggested that estrogenic therapy be given a trial. We have not used it in our cases.

CASE REPORTS

CASE 1 R W, a 41-year-old woman, was admitted to the hospital on January 25, 1948, complaining of pain and purulent discharge from the right third toe. About 8 months prior to admission the patient had noted pain in the right third toe, which was followed shortly by a moderate amount of purulent discharge from the ulcer at that site. At about the same time small areas of ulceration appeared over the malleoli and the lower tibial regions. The ulcers were quite painful, especially at night, and the patient experienced great difficulty in walking. For an indefinite period, moreover, she had difficulty in walking, although less severe, because of a "high arch," and she wore metal arches in her shoes. Treatment at the hospital afforded some relief, but the symptoms returned shortly after discharge.

The patient had been treated for diabetes for the past 7½ years. She took 15 units of regular insulin and 15 units of protamine zinc insulin in separate syringes in the morning. However, at the age of 23, when bilateral cataracts developed, routine examination of the urine revealed the presence of sugar. At that time she underwent a bilateral cataract extraction. Five years before entry glaucoma had developed in the right eye. Three years later this eye had become infected, and despite the use of penicillin she had lost the vision of that eye.

She had been told on numerous occasions that she had "pituitary and thyroid trouble." From about the age of 15 she had noted that the upper and lower extremities were very thin and that the skin of the extremities was "tight" and hard especially toward the distal regions. She had also noted the development of large "corns" over the bony prominences of the soles of the feet. Ulcerations developed relatively recently as noted above. She had had scattered gray hairs since the age of 32, she studiously dyed these as they appeared, and it was not possible to determine the extent of the canities. The hair had become more sparse in recent years.

In 1943 she noted a mass in the right breast and underwent a radical mastectomy for carcinoma. Since that time she had had no complaints because of the malignant growth.

The menses had begun at the age of 11. The periods occurred every 21 days and lasted for 7 days. The flow was rather profuse. For 2½ years prior to August, 1947, there had been no vaginal bleeding, but at that time she had a period. There was no further vaginal bleeding until her stay on the wards of this hospital, where she had a 3-day period of rather scanty vaginal bleeding. She had been pregnant once, with delivery after 7 months' gestation, the son was 7 years old and in good health. She believed her thinness had been aggravated during this pregnancy. She was legally separated from her husband, who was in a mental institution. She claimed normal libido. There were no symptoms referable to the cardiovascular, respiratory, genitourinary or gastrointestinal systems.

The parents of the patient were first cousins. The father had "kidney trouble" but was otherwise normal. Diabetes had developed in the mother at the time of the menopause, and she had died in diabetic coma at the age of 57, she had had asthma. The parents had no canities or any of the other signs of progeria manifested by the patient. The mother had three sisters, 2 of whom were diabetic and none of whom had gray hair, cataracts or the characteristic habitus of Werner's syndrome. The father had 3 half-sisters, all of whom were alive and well, and 2 brothers, of the latter, 1 had died during an intestinal operation, and the other of carcinoma of the throat. None of the father's siblings manifested the stigmas of the syndrome. The patient has a sister (Case 2) who suffered from similar symptoms. A brother

was completely normal. Three other siblings had died at birth, a fourth had died at the age of 2 weeks.

The patient weighed 102 pounds and was 4 feet, 10 inches in height. Her habitus was strikingly characteristic — spindly arms and legs, with a normally developed trunk. She had the typical bird-like facies resulting from a receding chin, tendency to beaking of the nose and the wearing of powerful lenses in her eyeglasses. Her gait was unsteady because of the atrophy of the muscles of the lower extremities and the high plantar arch, but she walked without any characteristic aberration. Her hair was diffusely sparse and was dyed black. She was of average intelligence and of rather cheerful disposition. No respiratory distress or asthenia was noted.

The right eye showed a buphthalmos (post-glaucoma), and the left a surgical coloboma. Some fibrosis of the lens bed was noted. The fundus seen through a +15 lens was slightly paler than normal, the vessels were moderately sclerotic, but there were no hemorrhages, exudates or pigmentation. The movements of the extraocular muscles were normal. There was mild circumferential injection of the left eye. The teeth were in good condition. The tongue was moist, with well developed papillae. The pharynx was clear. The ears were normal and did not project from the sides of the head in any unusual fashion. The eardrums were also normal. The eyelashes and eyelids were sparse. The voice appeared to be weak and somewhat high pitched (confirmed by the patient's statement), but indirect laryngoscopy did not reveal the hyperemic or keratotic changes described in this condition. The neck was supple. There was no distention of the veins, no tracheal deviation and no palpable thyroid gland.

The lungs were clear to percussion and auscultation. The heart was not enlarged, and the sounds were of fair quality. The aortic second sound was louder than the pulmonic. There was a Grade III, blowing systolic murmur over the entire precordium, maximal over the base, there were no thrills. Sinus rhythm was normal.

The left breast showed normal development, no masses or tenderness was noted. On the right side there was a healed mastectomy scar with no evidence of infiltration or tenderness in this region.

The abdomen was moderately obese and flabby. There was slight tenderness in the right upper quadrant, but no palpable masses or viscera.

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There was marked atrophy of the musculature of all the extremities, most pronounced in the distal segments, and this was accompanied by a moderate degree of weakness. The skin also appeared to be atrophic and over some of the terminal phalanges appeared to be tightly bound down to the underlying tissues, although true scleroderma was not present. Owing to the muscular atrophy the bony prominences of the fingers and toes were more prominent. The instep was markedly arched, and the patient used metal arches in her bathroom slippers for ambulation. There was bilateral hallux valgus. Callosities, the size of a 25-cent piece, were noted in the skin over the heads of the first and fifth metatarsals and over the calcaneus; these areas were not tender. On the right medial and the left lateral malleoli there were ulcerations about the size of a dime. These were excavations bordered by corn-like areas similar to those described above. The bases were greyish yellow, and there was no discharge. The areas were quite tender to the touch. Three scabrous callosities were also noted over the lower tibial areas. The tip of the third right toe was reddened, but no discharge was noted. There was no clubbing or edema. There were good pulsations of the posterior tibial and dorsalis pedis vessels.

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Rectal examination was negative.

Pelvic examination showed a parous introitus. There were no abnormal findings.

The temperature was 98.6°F, the pulse 80, and the respirations 20. The blood pressure was 110/70.

Examination of the blood revealed a red-cell count of 2,500,000, with a hemoglobin of 10 gm per 100 cc., and a white-cell count of 12,900, with 40 per cent neutrophils and

60 per cent lymphocytes. The sedimentation rate (Linzmeier method) was 18 mm in 45 minutes. The urine, which had a specific gravity of 1.010, gave a negative to +++ test for sugar, a negative test for albumin and a negative test for acetone, the sediment contained an occasional white cell. The blood sugar was 103 to 225 mg, the urea nitrogen 15 mg, the calcium 9.5 to 11.0 mg, the phosphorus 3.0 to 6.5 mg, the uric acid 3.4 mg, the creatinine 1.6 mg, and the cholesterol 200 mg per 100 cc., with 25 per cent cholesterol esters. The total protein was 6.8 gm per 100 cc., with 4.7 gm of albumin and 2.1 gm of globulin, and the carbon dioxide combining power 36 to 68 vol per cent. The urea clearance was 32 per cent. The phenolsulfonephthalein test showed 45 per cent excretion of the dye in 2 hours. The galactose tolerance test showed the excretion of 3.2 gm in the urine. The alkaline phosphatase was 1.6 Bodansky units per 100 cc. The cephalin flocculation and Mazzini tests were negative. The basal metabolic rate was +1 per cent.

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The patient had been treated for diabetes for the past 7½ years. She took 15 units of regular insulin and 15 units of protamine zinc insulin in separate syringes in the morning. However, at the age of 23, when bilateral cataracts developed, routine examination of the urine revealed the presence of sugar. At that time she underwent a bilateral cataract extraction. Five years before entry glaucoma had developed in the right eye. Three years later this eye had become infected, and despite the use of penicillin she had lost the vision of that eye.

She had been told on numerous occasions that she had "pituitary and thyroid trouble." From about the age of 15 she had noted that the upper and lower extremities were very thin and that the skin of the extremities was "tight" and hard especially toward the distal regions. She had also noted the development of large "corns" over the bony prominences of the soles of the feet. Ulcerations developed relatively recently as noted above. She had had scattered gray hairs since the age of 32, she studiously dyed these as they appeared, and it was not possible to determine the extent of the canities. The hair had become more sparse in recent years.

In 1943 she noted a mass in the right breast and underwent a radical mastectomy for carcinoma. Since that time she had had no complaints because of the malignant growth.

The menses had begun at the age of 11. The periods occurred every 21 days and lasted for 7 days. The flow was rather profuse. For 2½ years prior to August, 1947, there had been no vaginal bleeding, but at that time she had a period. There was no further vaginal bleeding until her stay on the wards of this hospital, where she had a 3-day period of rather scanty vaginal bleeding. She had been pregnant once, with delivery after 7 months' gestation, the son was 7 years old and in good health. She believed her thinness had been aggravated during this pregnancy. She was legally separated from her husband, who was in a mental institution. She claimed normal libido. There were no symptoms referable to the cardiovascular, respiratory, genitourinary or gastrointestinal systems.

The parents of the patient were first cousins. The father had "kidney trouble" but was otherwise normal. Diabetes had developed in the mother at the time of the menopause, and she had died in diabetic coma at the age of 57, she had had asthma. The parents had no canities or any of the other signs of progeria manifested by the patient. The mother had three sisters, 2 of whom were diabetic and none of whom had gray hair, cataracts or the characteristic habitus of Werner's syndrome. The father had 3 half-sisters, all of whom were alive and well, and 2 brothers, of the latter, 1 had died during an intestinal operation, and the other of carcinoma of the throat. None of the father's siblings manifested the stigmas of the syndrome. The patient has a sister (Case 2) who suffered from similar symptoms. A brother

was completely normal. Three other siblings had died at birth, a fourth had died at the age of 2 weeks.

The patient weighed 102 pounds and was 4 feet, 10 inches in height. Her habitus was strikingly characteristic—spindly arms and legs, with a normally developed trunk. She had the typical bird-like facies resulting from a receding chin, tendency to beaking of the nose and the wearing of poverial lenses in her eyeglasses. Her gait was unsteady because of the atrophy of the muscles of the lower extremities and the high plantar arch, but she walked without any characteristic aberration. Her hair was diffusely sparse and was dyed black. She was of average intelligence and of rather cheerful disposition. No respiratory distress or asthenia was noted.

The right eye showed a buphthalmos (post-glaucoma), and the left a surgical coloboma. Some fibrosis of the lens bed was noted. The fundus seen through a $\times 15$ lens was slightly paler than normal, the vessels were moderately sclerotic, but there were no hemorrhages, exudates or pigmentation. The movements of the extraocular muscles were normal. There was mild circumcorneal injection of the left eye. The teeth were in good condition. The tongue was moist, with well developed papillae. The pharynx was clear. The ears were normal and did not project from the sides of the head in any unusual fashion. The eardrums were also normal. The eyelashes and eyelids were sparse. The voice appeared to be weak and somewhat high pitched (confirmed by the patient's statement), but indirect laryngoscopy did not reveal the hyperemic or keratotic changes described in this condition. The neck was supple. There was no distention of the veins, no tracheal deviation and no palpable thyroid gland.

The lungs were clear to percussion and auscultation. The heart was not enlarged, and the sounds were of fair quality. The aortic second sound was louder than the pulmonic. There was a Grade III, blowing systolic murmur over the entire precordium, maximal over the base, there were no thrills. Sinus rhythm was normal.

The left breast showed normal development, no masses or tenderness was noted. On the right side there was a healed mastectomy scar with no evidence of infiltration or tenderness in this region.

The abdomen was moderately obese and flabby. There was slight tenderness in the right upper quadrant, but no palpable masses or viscera.

Neurologic examination was entirely normal.

There was marked atrophy of the musculature of all the extremities, most pronounced in the distal segments, and this was accompanied by a moderate degree of weakness. The skin also appeared to be atrophic and over some of the terminal phalanges appeared to be tightly bound down to the underlying tissues, although true scleroderma was not present. Owing to the muscular atrophy the bony prominences of the fingers and toes were more prominent. The instep was markedly arched, and the patient used metal arches in her bathroom slippers for ambulation. There was bilateral hallux valgus. Callosities, the size of a 25-cent piece, were noted in the skin over the heads of the first and fifth metatarsals and over the calcaneus; these areas were not tender. On the right medial and the left lateral malleoli there were ulcerations about the size of a dime. These were excavations bordered by corn-like areas similar to those described above. The bases were greenish yellow, and there was no discharge. The areas were quite tender to the touch. Three scabrous callosities were also noted over the lower tibial areas. The tip of the third right toe was reddened, but no discharge was noted. There was no clubbing or edema. There were good pulsations of the posterior tibial and dorsalis pedis vessels.

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Rectal examination was negative.

Pelvic examination showed a parous introitus. There were no abnormal findings.

The temperature was 98.6°F, the pulse 80, and the respirations 20. The blood pressure was 110/70.

Examination of the blood revealed a red-cell count of 2,500,000, with a hemoglobin of 10 gm per 100 cc., and a white-cell count of 12,900, with 40 per cent neutrophils and

60 per cent lymphocytes. The sedimentation rate (Linzenmeier method) was 18 mm in 45 minutes. The urine, which had a specific gravity of 1.010, gave a negative to $+++$ test for sugar, a negative test for albumin and a negative test for acetone, the sediment contained an occasional white cell. The blood sugar was 105 to 225 mg, the urea nitrogen 15 mg, the calcium 9.5 to 11.0 mg, the phosphorus 3.0 to 6.5 mg, the uric acid 5.4 mg, the creatinine 1.6 mg, and the cholesterol 200 mg per 100 cc., with 25 per cent cholesterol esters. The total protein was 6.8 gm. per 100 cc., with 4.7 gm of albumin and 2.1 gm of globulin, and the carbon dioxide combining power 36 to 68 vol. per cent. The urea clearance was 32 per cent. The phenolsulfonophthalein test showed 45 per cent excretion of the dye in 2 hours. The galactose tolerance test showed the excretion of 3.2 gm in the urine. The alkaline phosphatase was 1.6 Bodansky units per 100 cc. The cephalin flocculation and Mazzini tests were negative. The basal metabolic rate was -1 per cent.

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The past history included diabetes of 16 years' duration; the diagnosis had first been made during routine urine examination while the patient was undergoing treatment for a foot infection. The disease had been fairly well controlled on 10 units of regular insulin and 10 units of protamine zinc insulin taken in separate syringes in the morning. Three and a half years prior to admission a cataract developed in the right eye, and this was removed 6 months later. One year before admission a cataract extraction was done on the left eye. Vision had been poor. Glaucoma developed in the right eye postoperatively. The patient had had gray hair since the age of 40. Three years prior to admission ulcers on the legs entirely similar to those described in Case 1, as well as corns over the bony prominences on the soles of the feet, developed. The ulcers were painful, and she had great difficulty in walking. She stated that the legs felt very cold and she was bothered by cold weather.

The menses had begun at the age of 12, occurring every 28 days and lasting 2 or 3 days, during which there was scanty flow. There had been no menses since October, 1947. The patient had had an ectopic pregnancy in 1930, and she had not been pregnant since, although she had attempted to conceive. She claimed normal libido. Prior to admission she had been treated in the Cumberland Hospital Out-Patient Department for diabetes and leg ulcers, receiving for the latter various ointments and vitamin B₁ without benefit.

The resident who first examined this patient thought that she looked vaguely familiar but it was not until the second hospital day, when he found her talking to her sister who was on the ward at the same time, that the diagnosis became evident.

Physical examination revealed slight dyspnea while the patient was talking, but she was otherwise in no distress. She was exactly 5 feet in height and weighed 101 pounds. In appearance she seemed to be the twin of the patient in Case 1, both in facies and in habitus. The hair was scanty and gray. The eyebrows and eyelashes were also scanty. The movements of the extraocular muscles were normal. The scleras were clear. The right eye revealed surgical coloboma. The vessels of the fundus showed minimal sclerotic changes, there were no hemorrhages, exudates or papilledema. The left fundus was obscured by a cataract, although a cataract had been extracted on this side. The ears were normal in size and shape. There were no fat pads of the face or neck. The tongue showed well developed papillae. The pharynx was normal. The voice was normal, and indirect laryngoscopy revealed no changes. The neck was supple, with no distended veins, palpable masses or tracheal deviation. The thyroid gland was not enlarged. The lungs were clear to percussion and auscultation. Examination of the heart showed the point of maximum intensity in the fifth intercostal space within the midclavicular line. The sounds at the apex were distant and poor in quality. There was a soft, blowing systolic murmur at the apex. There were no thrills. The pulmonic second sound was louder than the aortic. There was normal sinus rhythm. The breasts showed normal development, with no masses. There was no rigidity, tenderness or palpable masses in the abdomen. No viscera were palpable. There was a well healed suprapubic midline surgical scar. The extremities were practically identical with those of the patient in Case 1, including atrophy of the muscles and subcutaneous tissue, small superficial ulcers over the right tendo achilles and over the base of the left fifth metatarsal, callosities over the heads of the first and fifth metatarsal bones and calcanei bilaterally and a marked hallux valgus bilaterally. The pulsations of the posterior tibial and dorsalis pedis vessels were excellent. The plantar arches were accentuated. The second, third and fourth fingers of both hands were markedly nodular and somewhat distorted, resembling the gnarled fingers observed in burnt-out rheumatoid arthritis. The joints were only slightly painful on firm palpation. There were slight sclerodermatous-like changes over the terminal phalanges of the fingers. There was normal distribution of the hair. The skin over the extremities was atrophic and slightly scaly. No telangiectatic changes were noted. Neurologic examination disclosed some unsteadiness in gait, as in Case 1, but again this was due to muscular weakness, painful leg ulcers and high plantar arches, there did not appear to be any neurologic background for the difficulties in gait, position sense and so forth was intact. Rectal examination was negative. Pelvic examination revealed a parous introitus. The cervix was pointed anteriorly. The fornices were normal. The fundus was not felt.

The temperature was 99°F, the pulse 105, and the respirations 24. The blood pressure was 114/70.

Examination of the blood disclosed a red-cell count of 4,200,000, with a hemoglobin of 13 gm per 100 cc, and a white-cell count of 9200, with 52 per cent neutrophils, 45 per cent lymphocytes and 3 per cent monocytes. The hematocrit was 44 per cent. The urine gave a negative to ++ test for sugar and negative tests for albumin and acetone. The blood sugar on three occasions was 142, 181.8 and 200 mg per 100 cc. The blood urea nitrogen was 12 mg, the uric acid 3.6 and 2.6 mg, the creatinine 1.5 mg, the calcium 11.0 mg, the phosphorus 3.0 mg, and the cholesterol 238 mg per 100 cc, with 70 per cent cholesterol esters. The total plasma protein was 7.2 gm per 100 cc, with 5.2 gm of albumin and 2.0 gm of globulin. The blood Kline and cephalin

flocculation tests were negative. The alkaline phosphatase was 1.0 Bodansky unit per 100 cc. The basal metabolic rate was -27 per cent.

X-ray examination of the chest revealed definite striation of the pulmonary fields, which was possibly due to some peribronchial thickening. There was marked decalcification of the bones of both feet, and considerable hallux valgus formation bilaterally, more marked on the left side, with almost complete inward subluxation of the bases of the proximal phalanges of the great toes from their articulations with the heads of the corresponding metatarsals. The intermetatarsal arteries showed appreciable calcification. There was moderate loss of calcium of all the bones of the carpo-metacarpal region and of the phalanges of both hands. Examination of the skull demonstrated granular osteoporosis, with neither direct nor indirect evidence of increased intracranial pressure. A small amount of lime was noted in the region of the pineal gland.

An electrocardiogram taken immediately on admission showed only left-axis shift and was identical with one taken 1 year previously in the clinic.

The patient soon ceased to complain of chest pain and, aside from the disability caused by the leg ulcers, was quite comfortable. She was placed on a diet of 200 gm of carbohydrate, 70 gm of protein and 50 gm of fat. She was treated with 15 units of protamine zinc insulin and 30 units of regular insulin mixed in one syringe in the morning. She was not overly co-operative in the matter of diabetic control, additional foodstuffs being found in her bedside table on several occasions, however, this did not seem to disturb her metabolic balance to any significant degree. She received therapy for the leg ulcers similar to her sister's. However, therapy was not administered over as long a period, and the response was not quite so satisfactory, she was discharged as "improved" on the same day as her sister. During her hospital course the temperature, pulse and respirations were within normal limits. A follow-up electrocardiogram showed no significant changes. The sedimentation rate was 55 minutes (Linzenmeier method).

DISCUSSION

It is hardly necessary to review the diagnostic criteria in these cases. A review of them leaves little doubt that they are classic examples of Werner's syndrome. We have had the opportunity of presenting them to Dr. Thannhauser, and he concurred with our diagnosis, stating that they were typical examples of the syndrome. Indeed, our 2 patients look like the twin sisters of the 2 brothers whom Dr. Thannhauser described in his exhaustive review article.

It is important to remember that the syndrome may not develop in all its features but may occur as a *forme fruste*. A knowledge of all the features of the syndrome is necessary to enable one to recognize the incomplete forms. It will be noted that our patients, like those reported elsewhere, were treated for many years by internists, ophthalmologists and general practitioners without the syndrome as a whole being recognized. We are quite sure that the disorder is not so rare as it appears to be. The advantages of the early recognition of a hereditary disorder are obvious.

SUMMARY

The criteria of Werner's syndrome are reviewed. Two cases of this syndrome are reported.

Attention is called to the presence of incomplete forms of this syndrome and the eugenic importance of early recognition of the syndrome in its complete or incomplete forms.

MEDICAL PROGRESS

PERIPHERAL VASCULAR DISEASE*

ROBERT R. LINTON, M.D.†

BOSTON

THIS report considers peripheral vascular disease under the two main divisions of diseases of the arteries and diseases of the veins

DISEASES OF THE ARTERIES

The surgical treatment of peripheral vascular diseases has made tremendous strides in recent years. The role that the sympathetic nervous system plays in the control of the arterial circulation of the extremities and the benefits derived by sympathetic neurectomy in many conditions are certainly to be included in great advances made in the therapy of peripheral arterial disease. Improvements in surgical technic, especially of blood-vessel anastomoses, the availability of blood transfusions through the establishment of blood banks and the development of the antibiotics, which have practically eliminated serious surgical infections, are other important factors in the widening of the scope of the surgical treatment of all vascular disorders.

Peripheral Arteriosclerosis

Arterial diseases secondary to peripheral arteriosclerosis are increasing in frequency because of the advancing age of the general population. The treatment of these conditions is becoming of ever-increasing importance because of this fact and since they represent one of the degenerative diseases that develop with old age.

The surgical therapy of peripheral arteriosclerosis of the lower extremities has become more of a surgical problem in recent years because of the improvement that can be obtained in the peripheral circulation by lumbar sympathectomy. This is especially true in patients that present themselves for treatment before actual gangrene of the extremity has developed. The chief indication for sympathetic neurectomy in these patients is the demonstration of normal or increased vasoconstriction or vasospasm. Various tests have been described to determine which patients will benefit by this procedure. Morton and Scott¹ used anesthesia, general, spinal or local, to determine vasomotor sympathetic activity. White² recommended paravertebral injections of procaine to block the sympathetic nerves. Gibbon and Landis³ described their method of reflex vasodilatation by heating the unaffected extremities or portions of the body. These

tests have been found to be of value in certain cases, but in others in which a negative response is obtained sympathectomy frequently improves the circulation. Smithwick⁴ described a test that is simpler and gives consistently more accurate results in determining which patients will benefit by sympathectomy. It consists in exposing the affected limb for an hour at a temperature of 68°F. If the skin temperature of the extremity reaches or approaches room temperature within a few degrees, under these conditions the presence of vasomotor activity is demonstrated and indicates that benefit will be derived from sympathetic neurectomy. Another simple clinical test that has been found of value is the observation of sudomotor activity in the extremity, which usually means that the blood vessels of the extremity will dilate if the vasomotor constrictor impulses are eradicated by an effective sympathetic denervation. Freeman⁵ has warned that in certain cases of advanced peripheral arteriosclerosis, especially those without evidence of normal vasoconstriction, sympathectomy may be detrimental because much of the blood may be shunted directly into the veins through the opening up of numerous small arteriovenous anastomoses. Burch⁶ and Goetz⁷ have recommended the use of a digital plethysmograph as a method of investigating peripheral vascular disease. They believe that with it exact information can be obtained about the degree of occlusion, the degree of vasospasm and the degree of collateral circulation. For practical clinical purposes, the method has not yet been proved, and at present it remains as a laboratory procedure for investigative studies in peripheral vascular disease. Another diagnostic procedure that has been recommended in recent years is arteriography. A roentgenographic visualization by the intra-arterial injection of a radio-opaque substance has been utilized as a diagnostic procedure for a number of years. Various types of solutions have been used. Shumacher⁸ and Kleinsasser⁹ recommend the use of 35 per cent diodrast solution. Each patient should be tested for sensitivity to the solution before it is employed. Visualization of the chambers of the heart, the pulmonary circulation and the great vessels has been successfully demonstrated by Robb and Steinberg,¹⁰ using 70 per cent diodrast solution. X-ray visualization of the abdominal aorta has been described by Wagner¹¹ and Nelson.¹² They recommend an 80 per cent sodium iodide solution

*From the Department of Surgery, Massachusetts General Hospital.

†Assistant clinical professor of surgery, Harvard Medical School, visiting surgeon, Massachusetts General Hospital.

It should be pointed out that arteriography is not without its dangers because of reactions from the drugs, which may in a few cases result in death and, in others, tragic ischemic difficulties in the injected limb. Arteriography should therefore be employed only when indicated and not as a routine in cases of arterial disorders. The most recent method of studying the peripheral arterial circulation is by means of radioactive isotopes. Smith and Quimby¹³ first reported the use of sodium 24 to show the level of adequate circulation in a limb and so determine the site of amputation in patients with obliterative arterial disease. Mufson et al,¹⁴ from the same clinic, used this method to determine the efficacy of drugs used in the treatment of peripheral vascular disease. Elkin and his associates¹⁵ have reported studies to determine the adequacy of peripheral arterial circulation using sodium 24 by intravenous and subcutaneous intramuscular injections. At the present time these studies and reports are extremely interesting, but further investigations with this new technic must be performed before the true value of the method can be determined.

The benefit of sympathectomy in the treatment of peripheral arteriosclerosis has been reported by a number of surgeons during the past year—Hendrick and Aycock,¹⁶ de Takats,¹⁷ Freeman⁵ and Yeager and Cowley.¹⁸ A careful selection of the patients subjected to this form of therapy should be made. The younger the patient is and the more evidence there is of vasomotor activity in the extremity, the greater the benefit that will be obtained. Intermittent claudication, as a rule, does not improve spectacularly after sympathectomy, but it has been observed to disappear gradually several years after the operation. The immediate benefit derived by sympathectomy is chiefly in the vascular supply to the integument. This in itself may be of great importance, since it will prevent the breaking down of the skin especially of the toes, which if it occurs frequently results in gangrene necessitating amputation. There appears to be definite evidence, however, not only that the extremity derives an immediate benefit from this form of treatment but also that it is the best protection that can be given to prevent serious vascular disorders with gangrene in old age. In other words, it appears at the present writing that the symptoms and signs of peripheral arteriosclerosis may be reversible if sympathectomy is performed early in the course of the disease and provided the sympathetic neurectomy is sufficiently extensive to prevent regeneration.

In the therapy of peripheral vascular disease there is a constant rivalry between the internist and the surgeon, the former to find nonsurgical methods of therapy to supplant surgical ones, and the latter to develop new surgical procedures. This form of competition should not be discouraged, but unfortunately too frequently some of the methods are

reported as the final answer to a problem without a sufficiently critical analysis of the results and procedures used. Both nonsurgical and surgical methods fall into this error. The chief criticism of the latter is that too many unqualified surgeons from lack of study and experience perform, with poor or disastrous results, surgical operations that have been established by authorities in their fields. This naturally discredits the procedure in the eyes both of many of the profession and of the laity. A number of nonspecific substances have been recommended for the improvement of peripheral arterial circulation during the past two decades. Some are given parenterally and others orally. These include the intravenous injection of a hypertonic solution of sodium chloride,¹⁹ or a nonspecific foreign protein (typhoid vaccine)²⁰ or diethyl oxide (ether)²¹, the intramuscular injection of sodium tetrathionate²², the oral administration of cytochrome C²³ or alpha tocopherol (vitamin E)²⁴, and finally the subcutaneous injection of histidine combined with the oral administration of ascorbic acid (vitamin C).²⁵ The beneficial effect on the peripheral circulation obtained by any of these methods, if it occurs, may only be transitory, and in most of the clinical reports other forms of therapy were utilized concomitantly on the patients, so that the improvement in the circulation cannot be attributed entirely to them. Borst and Holleman²⁶ have recently reported 3 cases of coronary thrombosis in 18 patients treated with intravenous sodium chloride solution and advise against its use.

Chemical sympathectomy by means of adrenergic and sympatholytic drugs has been utilized for many years without much success, but recently in this country it is being investigated with new drugs that show considerable progress in this field. Acheson and Moe,²⁷ in 1946, described tetraethylammonium chloride, or bromide, a ganglionic blocking agent. Nickerson and Goodman,²⁸ also in 1946, reported another drug, dibenamine (dibenzylbeta-chlorethylaminohydrochloride), which blocks the terminations of the sympathetic motor pathways in smooth muscle. Coller et al²⁹ and Lyons and his co-workers,³⁰ in 1947, reported the effects obtained with tetraethylammonium chloride in the diagnosis and treatment of peripheral vascular disease, including such conditions as causalgia, thromboangitis obliterans and thrombophlebitis. Both drugs produce peripheral vasodilatation, but their side effects are frequently so disagreeable that their clinical use seems somewhat limited and in some cases dangerous complications have been reported, one recently by Friedlich, Chapman and Stanbury.³¹ Priscol (2-benzyl 4, 5-imidazoline hydrochloride) is the most recent of these drugs to be employed in this country, although it was first reported in 1939 by Hartmann and Isler,³² and since then numerous reports of its clinical use have appeared in the European and South American medical litera-

ture Grimson,³² in this country, has recently reported the results in the use of this drug in a variety of peripheral vascular diseases, including Raynaud's disease, peripheral arteriosclerosis, thromboangitis obliterans, popliteal aneurysms, causalgia, acute arterial occlusion and venous thrombosis. It may be administered intravenously, intramuscularly or orally in doses of 25 to 75 mg. The results are sufficiently encouraging to warrant further investigation and clinical trial, but as yet it seems doubtful that a panacea for all these vascular diseases has been found. Chemotherapy for peripheral arterial diseases may eventually supplant sympathetic neurectomy, but at the present writing the latter, because of its more lasting effects and in most cases its few disadvantages, remains the best form of therapy in the majority of cases. Intermittent venous occlusion by the use of a pneumatic tourniquet cuff on the extremity, although of value in acute arterial occlusions, seems to have little if any benefit in the treatment of peripheral arteriosclerosis.

Despite the recent development of sympathectomy in the treatment of peripheral arteriosclerosis, amputations must still be performed in a certain number of patients. Improvements in technique are still being devised in the various types of amputations. Holden³⁴ again draws attention to the increased morbidity and mortality with toe amputations performed in this group of patients, many of whom require major thigh amputations because of failure to heal after the toe amputations. McKittrick,³⁵ on the other hand, has recently recommended transmetatarsal amputation in patients with gangrene secondary to lesions involving the toes in the diabetic patient with peripheral arteriosclerosis. This has proved to be a great advance in the surgical treatment of these patients, since it obviates an amputation at a higher level and preserves the foot with a surprisingly good functional result. He admits that the indications for this type of amputation are not yet completely clear, but they are continuing to be extended until a careful follow-up study of all patients satisfactorily demonstrates a clear-cut conception regarding whether it should or should not be undertaken. He points out that the use of this type of procedure has been greatly extended through the use of penicillin. Alldredge³⁶ reviews the surgery of amputations and reports some of the techniques of specific procedures. Silbert³⁷ recommends that the lower-leg amputation should be used more frequently than a mid-thigh or low-thigh amputation, since he claims that it reduces the mortality and because of preservation of the knee joint results in better function. Pearl³⁸ describes a modification of the supracondylar Calander type of amputation.

Thromboangitis Obliterans

Thromboangitis obliterans, or Buerger's disease, is the most common obliterative arterial disease

that affects the young male. Freeman³⁹ reported that the diagnosis was made in 274 of 3778 patients admitted to all the vascular centers during World War II. It is still a rare disease in the female. Only one probable case has been seen in a woman in the Peripheral Vascular Clinic of the Massachusetts General Hospital since it was organized in 1928. It rarely affects the Negro race, but in the last year Davis⁴⁰ and Breidenbach and Palmer⁴¹ have reported it in several Negroes. It is generally agreed that in the earlier cases sympathetic ganglionectomy offers the patient the best form of surgical therapy.⁴² Desensitization of the foot by means of crushing the peripheral nerves to it, described by Smithwick and White,⁴³ is still an important method of treatment in patients who present painful ulcerating lesions of the toes. This form of therapy not only relieves the patient of pain but also produces an improvement in the circulation since it sympathectomizes the limb distal to the level at which the nerves are crushed. Smoking, although not a definite etiologic factor, results in the progression of the disease in the majority of cases even in the sympathectomized extremity. Freeman³⁹ reports that in 77 patients who stopped smoking completely, there was progression of the disease in only 2, whereas in a group of 16 who admitted further smoking there was progression in 8. Adrenolytic and sympatholytic drugs, including tetraethylammonium chloride or bromide, dibenamine and priscol, are being used in various clinics in the nonsurgical treatment of this disease. Encouraging reports are appearing in the literature regarding this form of therapy, but as yet their true value has not been determined. It seems doubtful that they will replace sympathectomy, since the effect is only transient, whereas if the sympathectomy is performed properly a permanent vasodilatation is obtained.

Raynaud's Disease

Raynaud's disease characteristically affects the young and emotional person and is seen most frequently in women. Since the disease seems to be the result of an increased vasomotor activity in the sympathetic nervous system in a majority of cases and in only a few due to a local fault in the arterioles of the fingers, sympathectomy is the best form of surgical therapy. A preganglionic type of sympathetic neurectomy, as described by Smithwick,⁴⁴ is still the most generally accepted method of treatment. The results obtained for the upper extremity have not proved so lasting as those for the lower extremity.⁴⁵ For this reason further investigations are in progress in an attempt to improve the type of sympathectomy for the upper extremity. It is believed that a more radical and extensive ablation of the lower cervical and upper dorsal portions of the sympathetic nervous system should be performed. At the present time an attack on this problem along these lines is being car-

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doubtful Johns⁶⁵ compared the results of the suture and the nonsuture method for the anastomosis of veins in animals. He reported 90 per cent functioning patent end-to-side splenorenal anastomoses and 73 per cent end-to-end ones, utilizing the suture technic, whereas with the nonsuture vitallium tube method only 17 per cent were patent in a group of end-to-end splenorenal anastomoses. There seems little doubt that in venous anastomoses at least the suture technic is preferable because it reduces the danger of thrombosis from a relatively low differential pressure between the blood vessels and the slow rate of blood flow. It also permits the construction of an end-to-side anastomosis, which is not so feasible with the nonsuture technic. The use of the everting type of mattress suture to produce an intima-to-intima approximation in the anastomosis is recommended by most surgeons.⁶⁵⁻⁶⁶ The vessels must also be of sufficient caliber, otherwise thrombosis results in the majority of cases.⁶⁶ The utilization of rapid freezing permits the preservation of blood vessels indefinitely so that it is recommended that blood-vessel banks be established. The recent experimental work of Williamson and Mann⁶⁷ throws some doubt on the feasibility of such a project, since they report good results with autogenous transplantations of both arteries and veins, whereas they found that homogeneous transplantations are not justified in the light of present knowledge. Gross et al.,⁶⁸ however, have reported that chemically preserved blood vessels may be of value to bridge arterial defects.

Aneurysms and Arteriovenous Fistulas

Numerous papers reporting large series of aneurysms and arteriovenous fistulas have appeared in the recent surgical literature, the results of vascular injuries from missiles in World War II⁵⁵⁻⁶¹⁻⁶²⁻⁶⁹ and treated in the vascular centers established by the United States Army Medical Department. The advances in the treatment of these conditions have been chiefly through the utilization of sympathectomy to enhance the collateral circulation⁷⁰ and also in various types of blood-vessel repair and anastomoses. Another advance in the treatment of arteriovenous fistulas is that a number of surgeons have expressed the opinion and also demonstrated that if possible the continuity of an artery should be maintained⁷¹⁻⁷³ because the generally accepted method of treatment by quadruple ligation with excision of the fistula, although it restores normal vascular physiology of the body and preserves the limb, is always followed by a diminished blood flow to the extremity. The surgical therapy of the degenerative type of aneurysm secondary to arteriosclerosis has received added impetus because the incidence of it in various sites of the arterial system seems definitely to be on the increase. One of the most noteworthy contributions has been made by Blakemore,⁷⁴ who used a method of wiring and

electrothermic coagulation. Whenever possible the restoration of a pulsating arterial blood flow to an extremity, after the removal of an aneurysm, should be attempted, as a number of surgeons have demonstrated.⁷¹⁻⁷³ Blakemore⁷⁵ has adapted the nonsuture method of blood-vessel anastomosis, using the vitallium-tube cuffs and a vein graft inlay in the operation of restorative endoaneurysmorrhaphy for popliteal aneurysm. The external reinforcement of the aneurysmal wall by the application of cellophane has received considerable attention, since a number of apparently successful results have been reported.⁷⁶⁻⁷⁷ The true evaluation of the method, however, must await further experience and time. The application of cellophane around an artery proximal to an aneurysm for the purpose of gradual occlusion of the vessel has been attempted,⁷⁸ but the results have not been outstanding. Elkin⁷⁹ has recently re-emphasized the fact that aneurysms and arteriovenous fistulas may develop secondary to surgical procedures and warns against mass ligation of arteries and veins, especially transfixion sutures. Linton⁵⁰ has recently reported, as others have, the dire effects in the conservative treatment of the arteriosclerotic type of popliteal aneurysm and demonstrated the value of a preliminary sympathectomy followed later by an aneurysmectomy in the treatment of this condition.⁵¹⁻⁵³

The surgical treatment of congenital hemangioma in cases in which the area involved is not great is a simple procedure, but it is still a challenge to the surgeon if the lesion is an extensive one, when improvement rather than a cure is the best result that can be obtained.⁸⁴

Chronic lymphedema is the one peripheral vascular lesion in which little if any progress has been made since Kondoleon described his radical method of surgical excision of the diseased subcutaneous tissues. Minor modifications of this method appear now and then,⁸⁵ but further investigations and study are necessary to improve the results of the present forms of therapy, which at best are none too good.

DISEASES OF VEINS

Varicose Veins

Varicose veins of the lower extremity constitute one of the most common ailments affecting man. Therapy for this condition in the past for the most part has been inadequate because of recurrence or persistence of the varicosities. The injection of sclerosing solutions, it is generally agreed, gives only temporary benefit even when combined with a high saphenous interruption. It should be pointed out that this form of therapy also is not without its dangers. Boyd and Robertson⁸⁶ have reported that deep thrombophlebitis and incompetence of the communicating veins in the lower extremity may develop, and Vaughn and Lees,⁸⁷ in 1947, collected

ried out in the Peripheral Vascular Clinic at the Massachusetts General Hospital. The adrenolytic and sympatholytic drugs are also being used for the treatment of this condition in many clinics. As in thromboangitis obliterans, the results are somewhat encouraging, but the benefits derived persist only as long as the drug is used. Because of the high percentage of recurrence following the usual dorsal sympathectomy, these drugs are considered in a more favorable light than surgery in a number of clinics that are using them. Further experience is necessary, however, to determine their true value as a permanent form of therapy.

Peripheral Arterial Embolism and Thrombosis

Peripheral arterial embolism occurs most frequently in patients with auricular fibrillation and after acute myocardial infarction. The diagnosis as a rule is not difficult, but it is important to differentiate this disease from acute arterial thrombosis. The latter develops as a rule in elderly patients with advanced arteriosclerosis. The treatment of the latter should consist of conservative nonsurgical measures, such as the use of the anticoagulants heparin and dicumarol, and intermittent venous occlusion. Peripheral arterial embolism, on the other hand, is primarily a surgical disease in a majority of cases, and even a saddle embolus at the bifurcation of the aorta may be successfully removed, as demonstrated in recent years by a number of surgeons (Murray,⁴⁶ Linton,⁴⁷ Keeley⁴⁸ and Tendler⁴⁹). The most satisfactory surgical approach to peripheral emboli is a direct one to expose the artery at the point of embolization, even those of the aorta, as demonstrated by the above reports. Warren and Linton,⁵⁰ in 1948, reviewed the results in 179 arterial emboli in 98 patients. Surgical embolectomy saved 85.7 per cent of 21 limbs, whereas 65.8 per cent were preserved by conservative treatment. Arterial embolism is a true emergency, since if treatment, either surgical or conservative, is withheld for more than eight to ten hours the incidence of gangrene is greatly increased, owing to the formation of a distal propagated thrombosis from the site of embolism, if this condition develops, no therapy will re-establish the circulation to the limb.⁵¹ Surgical embolectomy should be considered and immediately performed provided a competent vascular surgeon is available. If not, conservative treatment with the anticoagulants and intermittent venous occlusion should be instituted at once.⁵² The patient should not be first subjected to the latter therapy and if it is not successful then turned over to the surgeon. Leriche⁵³ has recently reported the successful resection of the bifurcation of the aorta for arterial thrombosis of this large blood vessel. This appears to be a heroic procedure for a condition that might respond well to adequate lumbar sympathectomy. Therapeutic venous occlusion or the interruption

of the concomitant vein, when a major artery is severed, was first recommended by Makins⁵⁴ in 1919. During World War I it was ordered to be performed for major arterial injuries, whereas in World War II the benefit seemed so doubtful that it was not so ordered and was performed only in a relatively small number of cases.⁵⁵ A great deal of experimental work has been done to evaluate the effect of this procedure. At the present time there is experimental evidence that the blood inflow to an extremity is diminished using indirect measurements of blood flow,⁵⁶ whereas by means of direct methods utilizing the Rein thermistoruhr an actual increase has been observed.⁵⁷ The clinical application of therapeutic venous occlusion, utilizing the method of intermittent venous occlusion by means of a pneumatic venous tourniquet, has saved extremities that otherwise would have been lost from gangrene.⁵⁸ Its chief value is for extremities with an acute arterial occlusion, such as arterial embolism or arterial thrombosis, and it deserves a definite place in the therapy of such conditions. It must be begun within a few hours of the vascular accident, otherwise, intra-arterial thrombosis distal to the point of occlusion will result, and gangrene will develop regardless of the therapy used. It is probably of little or no benefit in the therapy of chronic or obliterative arterial diseases, such as that seen in peripheral arteriosclerosis and thromboangitis obliterans. It is believed that the beneficial effect obtained by the Pavaex (passive vascular exercise) method of Hermann and Reid⁵⁹ can best be explained by the fact that it probably causes intermittent venous occlusion.

Blood-Vessel Surgery

The recent interest in blood-vessel surgery to produce arterial and venous shunts has stimulated the experimental evaluation of the relative merits of the nonsuture and suture method of blood-vessel anastomoses. Blakemore and Lord⁶⁰ deserve much credit for stimulating surgeons in the practicability of blood-vessel repair and anastomosis utilizing the nonsuture vitallium-tube method. However, the results in the armed forces using it in battle injuries during World War II^{61, 62} were not outstanding because of the difficulty in getting the patient early, the necessity of working under battle conditions and, probably not least, the lack of training of the surgeons in this branch of surgery who had to use it under these conditions. Nevertheless, the method, at least in acute arterial injuries of the young, deserves a place in the field of vascular surgery and should not be completely discarded.

The use of absorbable fibrin tubes instead of vitallium ones for vein anastomoses has been advocated by Swenson and Gross⁶⁴ and reported results are extremely good, thrombosis having occurred in only 1 case out of 27. The availability of this type of tube for general use, however, seems

modifications consist of interruption of the superficial femoral vein, ligation and stripping of the long saphenous vein, excision of the short saphenous vein and a partial excision of the deep fascia of the lower leg, only one incision being used on the inner side of the lower leg

Venous Thrombosis and Pulmonary Embolism

During the last decade great interest has been shown in the prevention and treatment of venous thrombosis and pulmonary embolism. No longer is the attitude tenable that death from massive embolism is inevitable in a certain number of medical and surgical patients, or that expectant conservative treatment is satisfactory. Carotti et al,¹⁰³ in 1947, showed that pulmonary embolism and infarction occurred more frequently in medical than surgical patients, and also that 87 per cent of a series of 273 medical patients were over forty years of age. This agrees with Allen et al,¹⁰⁴ who showed that in 367 surgical patients with thromboembolism 82 per cent were in the same age group. Despite the fact that most cases of thromboembolic disease occur in middle-aged or elderly patients the young are not immune, as demonstrated by Zuschlag¹⁰⁵ and Myers and Artsis,¹⁰⁶ who report the occurrence of thromboembolism in children under fifteen years of age. Fatal embolism in this age group, however, is rare.

Pulmonary embolism from other sources is recognized. Of special interest are articles that have appeared in the last year reporting cases of maternal pulmonary embolism by contents of the amniotic fluid.¹⁰⁷⁻¹⁰⁹ The majority of the patients die, and the diagnosis is not made until autopsy. The condition apparently is rare, but it may be more common than it appears, since in one hospital 3 patients died from this cause and they represented all the maternal deaths occurring during one year.¹⁰⁸ Ingersoll and Robbins,¹¹⁰ in 1947, called attention again to the danger of oil embolism following hysterosalpingography.

Prophylaxis Greater attention should be directed to the prophylaxis of venous thrombosis because deaths from massive pulmonary embolism still occur in patients without clinical evidence of deep venous thrombosis. Evans¹¹¹ reports 54 deaths from fatal embolism under these conditions in a series of 238 cases of postoperative thromboembolism, an incidence of 23 per cent. Allen,¹¹² in 1947, demonstrated the value of prophylactic interruption of the femoral vein in a series of 458 patients over sixty-five years of age, as compared to a comparable group of patients who received no special prophylactic therapy. In the former there was 1 death from massive pulmonary embolism, whereas in the latter there were 26 deaths from the same cause. At the present time there are no statistics that demonstrate that prophylactic use of dicumarol or heparin will give the same or better

protection in this aged group of patients in which thromboembolism is so prone to develop. Allen,¹¹² Bishop¹¹³ and Golodner et al¹¹⁴ have drawn attention to the relatively high incidence of fatal embolism in elderly patients with fractured hips, and recommend prophylactic measures such as interruption of the femoral vein or the use of anticoagulants. Veal¹¹⁵ has stressed the importance of interruption of the femoral vein in thigh amputations for the prevention of pulmonary embolism.

The prophylactic use of dicumarol has also been demonstrated to be of value in the average post-operative patient. Smith and Mulligan¹¹⁶ reported its use in 2353 surgical patients with only 1 death from fatal embolism. Allen¹¹⁷ reported the effect of dicumarol in 647 patients between forty and sixty-five years of age undergoing major surgical operations, without a single death from pulmonary embolism. Barker et al¹¹⁸ and Murray,¹¹⁹ in 1947, likewise reported 100 per cent protection by the prophylactic use of the anticoagulants in the post-operative patient. It should be pointed out, however, that the use of dicumarol in this manner is not without its dangers, since Allen¹¹² reports 2 deaths and Smith¹¹⁶ 1 from hemorrhage.

Treatment Homans,¹²⁰ in 1934, was the first to recommend interruption of the femoral vein for the treatment of venous thrombosis and pulmonary embolism. Since then numerous articles on the subject have appeared in the surgical literature. Allen and his associates¹²¹ at the Massachusetts General Hospital have demonstrated the efficacy of bilateral femoral-vein interruption in the treatment of venous thrombosis and the prevention of massive pulmonary embolism by this method. Other surgeons¹²²⁻¹²⁵ agree that this method is of value, especially in patients who have had nonfatal pulmonary emboli, to prevent fatal embolism. Carloti et al¹⁰³ also showed a reduction in the over-all mortality in cardiac patients with thromboembolic disease who were subjected to bilateral femoral-vein interruption, as compared to a control group not so treated.

It should be emphasized that interruption of the femoral vein if performed by capable surgeons is a safe procedure, but it is not without its dangers for the average surgeon, as pointed out by Sarnoff,¹²⁶ who reports a case of gangrene of both legs following the procedure. Dennis¹²⁷ also reports serious impairment of the circulation after interruption of the common femoral vein and the saphenous vein in the same extremity. It is believed that if femoral-vein interruption is to be performed, the interruption should never include the common femoral vein and the saphenous vein, since under these circumstances there may be insufficient collateral venous return from the extremity, as demonstrated in the report by Dennis.¹²⁷ In competent hands it is recommended that if a clot is found in the common femoral vein, the interruption of this vessel be performed after thrombectomy distal to the saphenofemoral

44 cases of fatal pulmonary embolism following injection therapy Smith and Johnson,⁸⁸ in 1948, reported from the Mayo Clinic 17 nonfatal pulmonary emboli and 1 death following this treatment in 11,700 patients. In the same year Luke and Miller⁸⁹ collected 4 additional fatal cases and 10 other cases of deep thrombophlebitis after ligation and injection of the saphenous vein. Accidents following the operative treatment have also occurred. Luke and Miller⁸⁹ also report several cases of ligation of the femoral artery or vein instead of the saphenous vein, and in 1 case injection of the distal femoral artery with the sclerosing solution resulting in gangrene of the extremity. Many similar unreported accidents have occurred undoubtedly (I know of 6 patients in whom the femoral artery was ligated and divided instead of the saphenous vein). The procedure of high interruption of the saphenous vein should not be condemned because of these mistakes since they were the result of poor surgery. New types of sclerosing solutions continue to appear in the surgical literature. The most recent one, sotradecol (sodium tetradecyl sulfate),⁹⁰ has certain advantages over the older ones, but it will not cure varicose veins without surgical removal of the main saphenous trunks. High interruption with retrograde injection of the sclerosing solution perhaps gives better results than injection therapy alone, but few patients obtain permanent relief. Because of the poor results by these forms of therapy, there has been during the past few years the revival by a few surgeons (Hodge,⁹¹ Prioleau,⁹² Vaughn,⁹³ Summers,⁹⁴ Sherman⁹⁵ and Linton⁹⁶), of high interruption and removal of the saphenous veins, both long and short, by stripping or excision. The stripping of varicosities was first recommended by Mayo⁹⁷ and Babcock.⁹⁸ The intraluminal type of stripper described by the latter has proved to be the more satisfactory, since with its use the vein can be removed more readily and completely. Unfortunately, many patients will continue to have the injection treatment, only to come finally to the surgeon for more radical therapy. The results in these cases are never so good as those in the patients who have not been treated with injections, since it is often difficult to remove the saphenous veins completely because of local areas of fibrosis and obliteration, which prevent insertion of the stripper and the complete removal of the main saphenous trunks. In addition the valves of the communicating veins, especially in the lower leg, become incompetent, the result of the sclerosing solution damaging these structures, so that in these patients recurrences are more prone to develop. It is my opinion that the most satisfactory therapy is ligation of the long saphenous vein at the saphenofemoral junction with the removal of the main trunk of this vein by stripping from the groin down to a point just distal to the internal malleolus. In a few cases excision of

some of the large tortuous varices may be necessary, and in some the saphenous trunk may be bifid, in which case both are removed. If the short saphenous vein is incompetent it should be removed also, after ligation at the saphenopopliteal junction, by stripping it to the level of the external malleolus. The stripping procedure is best performed under a general anesthetic to obtain the most radical removal of these veins. In most cases only a few injections of a sclerosing solution are necessary in the few remaining varicosities. These, for the most part, are for cosmetic effect.

Simple Varicose Ulcers

The cure of simple varicose ulcers due to varicose veins, in essence, consists of eradication of the varicosities. Numerous types of ointments have been recommended for the cure of this condition, but none, even those including the antibiotics and sulfonamides, have any special virtues. The use of these drugs should be discouraged since their topical application frequently sensitizes the patient to them so that their parenteral use at a later date, when they are needed for serious infections, may be prohibited owing to an acquired sensitization.

Post-Thrombotic Varicose Ulcers

The cure of this distressing type of ulceration remains a serious problem. Numerous methods of therapy have been recommended but few give better than temporary healing. The application of a gelatin-paste (Unna) boot or an elastic adhesive bandage (elastoplast) will heal, at least temporarily, the majority of these ulcers. These methods should be used chiefly to prepare the extremity for surgery by healing the ulcer and as postoperative dressings for periods of a few weeks to months. A new type of operation recently developed for the less extensive ulcers includes interruption of the superficial femoral vein, with ligation and stripping of the long and short saphenous veins. Buxton and Coller⁹⁹ and Homans¹⁰⁰ were the first to suggest interruption of the femoral veins. Linton and Hardy⁹⁶ have reported good results in a number of patients combining superficial femoral-vein interruption with radical stripping of the long and short saphenous veins. Further experience and a longer follow-up study on these cases are needed before a true evaluation of this method can be obtained. The method described in 1917 by Homans,¹⁰¹ consisting of radical excision of the ulcer with an immediate split-thickness skin graft, still deserves a place in this field of surgery, especially in the large indolent ulcers. The superficial femoral vein should be interrupted also if this procedure is performed, and the saphenous veins removed if they are large and incompetent. In some cases a less disfiguring operation, described by Linton¹⁰² in 1938, has given excellent results. The operation has been modified somewhat since it was originally described. These

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junction and proximal to the origin of the profunda femoris vein. If no clot is found, in the majority of cases interruption of the superficial femoral vein just distal to the profunda femoris will suffice. Interruption of the inferior vena cava is chiefly indicated, as pointed out by a number of authorities,¹²³⁻¹³¹ for pulmonary emboli arising from pelvic thrombophlebitis, especially the septic variety. It should not be performed for the usual case of thromboembolic disease, since it is a major surgical procedure that may carry a relatively high mortality, as demonstrated by Thebaut,¹³² and in most cases it is an interruption of the venous system at a level higher than necessary to prevent further pulmonary emboli.

The treatment of deep venous thrombosis by procaine block of the lumbar sympathetic nerves, as recommended by Ochsner,¹³³ is of chief value in patients with the obstructing type of femoriliac thrombosis to relieve pain and swelling. It does not necessarily protect the patients from pulmonary embolism.

The use of the anticoagulants in the treatment of thromboembolism has received great impetus also, especially since dicumarol has become so readily available. Heparin was the first anticoagulant to be used and is still recommended by some authorities (Murray,¹¹⁹ Bauer,¹³⁴ Jorpes,¹³⁵ Loewe¹³⁶ and Evans¹³¹). The chief exponents of heparin have been in the Canadian and Swedish schools. Loewe,¹³⁶ in this country, has developed a preparation that is slowly absorbed and is given intramuscularly. Despite the fact that it is the ideal anticoagulant yet developed because of its rapidity of action and its ease of control, heparin has not found wide usage on account of its expense. Dicumarol, more recently discovered, is now more generally used because it is cheap and may be given orally.^{118, 127, 128} It is generally agreed that it should not be used unless laboratory facilities are available for the accurate determination of the prothrombin time. It is significant to note that deaths still occur from massive pulmonary embolism in clinics that treat patients with the anticoagulants after a diagnosis of venous thrombosis with or without pulmonary embolism has been made.^{109, 118, 136, 141} The same drawback to the treatment by femoral-vein interruption has also been reported by Allen¹¹⁷ in a large series of cases, so that at the present time there is no method that will prevent massive pulmonary embolism in 100 per cent of the patients. In conclusion, it appears that the safest method of treatment, once thromboembolism has developed and is recognized in any patient, is to perform bilateral femoral-vein interruptions and to supplement this treatment by anticoagulant therapy.

Portal Hypertension with Bleeding Esophageal Varices

One of the important advances in peripheral vascular surgery in the last few years has been the

treatment of bleeding esophageal varices secondary to a portal bed block, either of the intrahepatic type (portal cirrhosis) or the extrahepatic (the so-called Banti's syndrome) by the construction of various types of venous shunts between the portal and the general venous systems. Whipple¹⁴² and Blakemore¹⁴³ deserve great credit for this renewed attack on a problem that has long baffled the medical profession. They first recommended as the operative procedure a splenectomy, a left nephrectomy and an end-to-end nonsuture anastomosis between the splenic and renal veins. In 1947 the operation was modified by an end-to-side suture type of splenorenal anastomosis with preservation of the kidney as recommended by Linton et al.¹⁴⁴ Direct anastomoses between the portal vein and the inferior vena cava, both end-to-side and side-to-side, have been performed safely a number of times by Blakemore.¹⁴⁵ Further experience and observations of these patients with portacaval shunts are necessary before a true evaluation of this form of treatment can be determined. Furthermore, the relative merits of splenorenal, end-to-side portacaval and side-to-side portacaval anastomoses have yet to be determined. It appears quite definite, however, that a surgeon should not perform a splenectomy alone for bleeding esophageal varices, especially of the extrahepatic (Banti) type, since this may be the only opportunity at which a satisfactory venous shunt can be performed.¹⁴⁶

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

CASE 35161

PRESENTATION OF CASE

A ten-year-old girl was admitted to the hospital because of a progressive swelling in the neck.

She was seen for the first time five months before admission in the Out-Patient Clinic. The cervical mass, then of two months' duration, had not been accompanied by any systemic symptoms. There was no change in weight, appetite or bowel habit. No unusual sweating was noted, nor was there any preference for cold or warm weather. There was no tremor or exophthalmos. The patient is said to have frequently cleared her throat "as though she had some obstruction" after the mass appeared, but she had no difficulty swallowing. Two years before admission her mother noted that the patient's emotional pattern had changed: she became unhappy, cried easily and was "less peppy" than she had previously been. These changes persisted.

The patient's mother had had a goiter during pregnancy and for some months thereafter. She received 5 drops of an iodine solution daily for about a year altogether. Iodine was taken during the entire period of pregnancy.

The patient's maternal grandfather had had an operation for hyperthyroidism.

On examination the thyroid gland was diffusely enlarged and not nodular. The left lateral lobe was more easily palpable than the others. There were no other abnormal findings. The temperature was 97.8°F, the weight 66 pounds, and the height 53 inches. X-ray examination of the wrists demonstrated that the bone age was not at variance with the chronologic age. The blood cholesterol was 200 mg per 100 cc.

The patient was seen regularly in the Out-Patient Department. The mass in the neck persisted and increased in size. Three weeks before admission the gland was diffusely and evenly enlarged. The right lobe, particularly the upper pole, was prominent. The enlargement was firm and granular. Lymph nodes were enlarged, two Delphian and one of the posterior chain on each side. On the same day the decision was made to admit the patient for a surgical biopsy and possibly a more extensive procedure.

On admission the child was quiet and sad, crying on the slightest provocation. The thyroid gland was estimated to be twice its normal size, diffusely enlarged, granular and firm. There was no generalized lymphadenopathy.

The temperature was 99°F, the pulse 86, and the respirations 20. The blood pressure was 98 systolic, 68 diastolic. The height was 54 inches, and the weight 64 pounds.

The urine was normal. The white-cell count was 5600, with a normal differential. The hemoglobin was 12.9 gm. After a barium swallow the esophagus was questionably displaced to the left in the region of the thyroid gland. There was no obstruction to the flow of barium through the esophagus and no evidence of any substernal extension of the thyroid gland.

In the opinion of the last examiner in the Out-Patient Clinic there was definite change in the gland during the three-week interval. It was smaller, and only the right upper pole retained its abnormality; the isthmus and left-lobe processes had receded. The Delphian node and the enlargement of the right-posterior-triangle lymph node persisted.

Operation was deferred in lieu of further clinical observation. Radioactive iodine was administered. There was a 39 per cent uptake in the gland, which was interpreted as the upper limit of normal.

She was discharged on the third hospital day.

Second admission (ten weeks later). During the interval the patient was followed in the Out-Patient Department. Several observers felt that the thyroid gland progressively increased in size during subsequent weeks. She gained about 5 pounds and felt well.

Except for the findings in the neck, there were no changes on physical examination.

On the third hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR J H MEANS: This the first time at one of these conferences that I have been given a case that seems to be goiter. Perhaps it is not a goiter, but it appears to be.

I will make a few comments on the history, then if there is other evidence, we will ask for it and attempt to make a diagnosis. It is apparently clear that this girl had a goiter. I do not believe we need consider other enlargements in the neck. Let us say that it was a goiter. The descriptions fulfill that definition perfectly well. It is interesting that she had no symptomatic changes early in the history, but a change of personality is described. She had crying and depression, which might be seen in Graves's disease. There is little else to suggest Graves's disease, however. Whether or not the mother had a goiter during pregnancy is not perfectly clear. I think that any physician who has a patient going through pregnancy with a thyroid

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case in which it was proved that a cancer of the colon had metastasized to the thyroid gland. Lymphoma may involve the thyroid gland diffusely and apparently without much lymphoma elsewhere, so that lymphoma must be considered. There is one type of non-neoplastic disease that must be mentioned—that is amyloidosis. We have had 4 or 5 cases of amyloid disease of the thyroid gland. I do not believe that amyloidosis was present in this case. In fact, I will rule it out, although we have no right to rule it out absolutely because there has been nothing said about a Congo-red test. Amyloidosis of the thyroid gland might be part of what we call idiopathic amyloidosis, but I would expect lesions elsewhere. A chronic, suppurative process or tuberculosis we cannot throw out, but I think it is entirely unlikely.

Of the primary tumors of the thyroid gland I do not believe it is any kind of benign tumor because I would expect that to be nodular, at least in the beginning. Benign tumors of the thyroid gland do not start, in my experience, as a diffuse process. They may become so later by multiplicity of nodules closing together to give the appearance of a diffuse lesion. I think that is unlikely and I therefore believe the diagnosis lies between some kind of chronic thyroiditis and some kind of malignant tumor, which might be epithelial. There are various types of adenocarcinoma of the thyroid gland, papillary and otherwise, and some highly undifferentiated cancers. I do not think we need to go into the classification of the various types of tumor because one cannot possibly make a differentiation except histologically. As between chronic thyroiditis and a malignant process the regional lymph nodes strongly suggest a malignant process but we have found the Delphian node, so-called, in chronic thyroiditis, so that that is not absolutely of differential diagnostic value. The mass has never been tender so far as we know. Sometimes these chronic processes are not. There is nothing in the story suggesting an acute thyroiditis, but our general concept of the chronic forms is that they are not an aftermath of an acute type but an independent condition generally of a different etiology in all probability. As between the two types I have mentioned, the lymphadenoid type of chronic thyroiditis or Hashimoto's struma and Riedel's struma I would think that the former was more likely simply because it is more common. The Riedel type is very rare, and the description of this gland does not sound like it. It is not described as stony hard. It was firm and granular. I do not know what is meant by granular. I never felt a thyroid gland that I would call granular. The choice lies, I believe, between Hashimoto's struma and some kind of malignant goiter, but I have not the faintest idea which it was. It was not growing very rapidly, which would make it possible to rule out a highly undifferentiated cancer. The

regional lymph nodes are frequently involved in papillary types of thyroid cancer but I would not rule out lymphoma even in the absence of a lymphoma elsewhere. So I am going to leave it as a choice between Hashimoto's struma and a rather diffuse malignant tumor of the thyroid gland, and I think on the chances, a papillary adenocarcinoma would be more likely than any other kind. I am prepared to be told, however, that it is either or neither of them. What is needed here is histologic evidence so far as I am concerned.

DR CASTLEMAN: Are the x-ray films helpful?

DR STANLEY M. WYMAN: They are not contributory.

DR TALBOT: Like Dr Means, we came to the conclusion that this child probably had either thyroiditis or a neoplasm of the thyroid gland. Not wishing to run the risk of neglecting a neoplasm while it still might be amenable to therapy we urged surgical biopsy examination. In this connection we also thought that should the diagnosis turn out to be thyroiditis, there might be some prophylactic value in excising a portion of the thyroid isthmus since there is some tendency for thyroiditis to result in constriction of the trachea and adjacent structures. Perhaps Dr Means would like to comment on this subject.

DR MEANS: About the matter of constriction from chronic thyroiditis particularly the Riedel type, it may produce severe tracheal obstruction, but so may the Hashimoto type and a partial resection may have to be done to remove pressure symptoms. This child apparently was getting slight pressure symptoms. In this type of goiter, if it is Hashimoto's, being a lymphadenoma type of thing, one might get good results with x-ray therapy. One does not operate on Hashimoto's struma unless there is an indication for relieving pressure.

That was one other point I did not discuss much. It puzzled me a little whether this posterior gland was part of the same process or a red herring. I was not sure.

DR TALBOT: It was just posterior to the thyroid gland itself.

DR MEANS: Quite close to the thyroid gland. I suppose that would favor a little bit the diagnosis of a malignant process because I would expect one might find a Delphian node with thyroiditis, but I would not expect it so much in the lateral region. Another thing is that the gland in Hashimoto's struma is sometimes described as being more or less like an ameba, with pseudopodia sticking out. One can feel scallops at the edge of it, and that is not mentioned here so I am a little bit more inclined to think that it was malignant but I am not at all sure. That just gives it a little edge.

CLINICAL DIAGNOSIS

Chronic thyroiditis, Hashimoto type?
Carcinoma of thyroid gland?

enlargement does well to give iodine, particularly if there is any evidence of hyperfunction during pregnancy, more than would be explained by the pregnancy itself. I also have the feeling that when women who are pregnant have low metabolism they should be given thyroid. I cannot get any more out of that information than just that, nor can I place any great amount of weight on the fact that the patient's maternal grandfather had an operation for hyperthyroidism. I would like to know more about the family situation, however. I would like to know where the patient was born, where her parents were born and where this operation on her grandfather was done. I would like to know also whether she did or did not come from an endemic goiter region.

DR BENJAMIN CASTLEMAN Both she and her mother were born in Massachusetts.

DR MEANS We do not know where in Massachusetts, but we know that the goiter region in Massachusetts is in the Berkshires, where minimal thyroid enlargement has been found among school children.

DR CASTLEMAN She came from Cambridge.

DR MEANS It is stated that the thyroid gland was enlarged and not nodular. It is important to know whether it was a diffuse goiter or a nodular goiter. We have to take this story at face value, it was diffusely enlarged, and no nodules were felt.

Laboratory examination showed a blood cholesterol within normal limits. The finding of enlarged lymph nodes is of importance, the so-called Delphian node. One of the students suggested calling it that to Dr Cope. The point was that since the Delphian oracle foretold things, and the node just above the isthmus may enlarge when some process is going on in the thyroid gland, it is a tell-tale node. Sometimes one confuses an enlarged pyramidal lobe with a lymph node. I assume that there were enlarged nodes and some of them were in the posterior triangle. Also quite important is the negative evidence that no adenopathy was found elsewhere. There is no mention of splenomegaly or hepatomegaly or anything of that kind. The radioactive-iodine collection was at the upper border of normal, and I will say that it probably was normal. I will conclude, therefore, from that much of the history and the physical findings and that one bit of laboratory evidence, that this patient had a goiter causing no disturbance in function — that is, a state of euthyroidism. I wonder why they sent her in for a biopsy and out without having it done. That is not clear. I wonder why they waited for ten weeks. Perhaps the family refused or it took them ten weeks to convince those in charge that it was indicated. Is that a fair question?

DR CASTLEMAN Can you answer that, Dr Talbot?

DR NATHAN B TALBOT I was anxious to have a biopsy done, but it was difficult to persuade the surgeons.

DR MEANS All I can say, then, is that I do not know why they sent her in for a biopsy and then did not do it, because it might have made the diagnosis. The most important thing in diseases of the thyroid gland, as of any other part of the body, is to establish a diagnosis. When one sees an enlarged thyroid gland, particularly when it is not giving rise to any change in function, one almost always has to have a histologic examination. That is the only way to determine its character. If one is dealing with a full-blown picture of Graves's disease, one knows what the thyroid gland will show and does not have to worry about the histologic diagnosis. There are no other laboratory tests recorded in this history, such as the protein-bound iodine. I suppose they were normal, but if they were not done, I would not worry about them because the clinical evidence for euthyroidism is quite impressive. I do not know what was going on during the ten weeks' observation when the gland was smaller, not larger. I do not know how to interpret that. I do not know from the record whether or not the goiter was larger at the time of operation than at the time the patient was first seen. Is that a fair question? Whether it had increased in size or remained stationary is all important in making a differential diagnosis.

DR TALBOT There were differences of opinion about the size of this gland as time progressed.

DR MEANS It is evident that it was not growing at a great speed. I do not believe they said whether or not it was tender.

DR TALBOT It was not tender.

DR MEANS They finally did an operation. Whether it was a biopsy or a radical neck resection, I do not know. There was a surgical procedure, which, I suppose, disclosed a diagnosis. What must we consider? I think we have to consider every kind of goiter in differential diagnosis. I will try to be brief. I think we can rule out Graves's disease. The question whether or not it is endemic goiter would come up, but I would dismiss it because she did not come from an endemic region. A goiter due to cabbage or goitrogenic drugs might be considered. Did she have any of these things?

DR TALBOT No.

DR MEANS Another possibility is tuberculosis of the thyroid gland. I cannot exclude that. I do not know whether we have ever seen a case at this clinic. It is extraordinarily rare. We are now down to some kind of neoplasia or some kind of chronic inflammatory process. It seems to me this case could be one of the forms of chronic thyroiditis such as Hashimoto's struma or Riedel's struma. It could be any one of a considerable variety of tumors. One thinks of primary tumors, of course, although metastatic tumor to the thyroid gland does occur. We have had 2, I think perhaps 3, cases of hypernephroma that metastasized to the thyroid gland. When I was in California a year ago I was told of a

day penicillin was started and the sulfadiazine discontinued. During the next two to three days the urine output dropped to 60 cc per day, and the nonprotein nitrogen was found to be 60 mg per 100 cc. At this time the carbon dioxide was 24.5 milliequiv per liter, and the sulfadiazine level was 13.2 mg per 100 cc. The total protein was 5.9 gm per 100 cc. The prothrombin time was 33 seconds (normal, 16 seconds). The clotting time was 18 minutes, and the clot retraction was normal. The joint pains, which had been quite bothersome, began to subside, and the temperature returned to near normal. The nonprotein nitrogen continued to rise, being 90, 106 and 150 mg per 100 cc on the fifth, sixth and seventh hospital days. The urinary output was still low (150 cc per day), and disorientation was a prominent symptom. At this time the hemoglobin was 10 gm, and the white-cell count 7200, with 76 per cent neutrophils, 2 per cent young polymorphonuclears and 1 per cent blast forms. A blood culture revealed no growth. A few petechiae appeared over the trunk and extremities. On the eighth hospital day the urinary output began to increase, but the nonprotein nitrogen continued to rise, and a to-and-fro friction rub was then heard over the anterior chest, being loudest over the second and third interspaces on the left. By the ninth hospital day the erythematous rash had faded considerably. She became dyspneic and drowsy, and twitchings occurred at intervals of one second. On the thirteenth hospital day the nonprotein nitrogen had risen to 200 mg per 100 cc. A platelet count at this time was 58,000. The urine gave a +++ test for albumin, and the sediment contained 50 red blood cells and 6 white blood cells per high-power field. A swelling developed over the left parotid region. On the fifteenth hospital day the nonprotein nitrogen was 280 mg per 100 cc. The patient was comatose and exhibited choreiform movements. A uremic frost appeared on the forehead and lips, and she died later that day.

DIFFERENTIAL DIAGNOSIS

DR ALFRED KRANES: Have you any idea what form this patient's sensitivity took? Was it asthma?

DR MARIAN ROPES: It was simply sneezing, with no real asthma.

DR KRANES: We are faced with the ever-recurrent problem of trying to predict the histologic picture of a kidney in a patient who obviously died of renal insufficiency and uremia. By and large, that is not likely to be a very accurate clinical exercise, but there is no reason why we should not keep trying. In this case we are limited, it seems to me, to consideration of only the acute forms of renal disease, since this patient's illness lasted exactly one month—unless one wants to make the assumption, hardly justified by the facts given here, that this represents an acute exacerbation of some chronic renal disease. From the information available there is no reason

to think that this patient had pre-existing renal disease. The original urine examination, with a specific gravity of 1.022, indicates good function of the kidneys, although no other renal-function tests are given. So I will limit myself to a discussion of certain types of acute, rapidly fatal kidney disease.

We can eliminate from our discussion any of the acute poisonings such as mercury, arsenic or carbon tetrachloride since there is no reason from the history why we should consider them seriously. The most common acute renal disease that will produce this type of picture is acute glomerulonephritis, and there are many parts of this picture that can be well explained by such a diagnosis. Certainly, the hematuria, the oliguria, the pulmonary edema that developed and the eventual uremia and death are readily explainable on this basis. However, several aspects of the picture are a bit unusual. In the first place, nothing is said about the finding of any casts in the urine, although they may have been present. One would expect a patient with acute glomerulonephritis to have a fair number of casts in the urine.

DR WALTER BAUER: She had frequent granular casts on one specimen only.

DR KRANES: One would expect more than that. We are given only one blood pressure reading of 120 systolic, 68 diastolic. Nothing is said about the subsequent course of this patient's blood pressure. I am assuming that there was no appreciable change, but that assumption may be wrong. If the blood pressure showed no rise, it certainly would be strong evidence against the diagnosis of acute glomerulonephritis. But what bothers me even more about such a diagnosis is the early part of the history: the degree of fever, and the amount of pain in the calves, thighs and joints. Did this patient have much joint pain in the upper as well as the lower extremities?

DR ROPES: Not as much in the upper extremities. She definitely had joint pain occasionally over the course of two or three years, usually in the upper extremities. About six or eight months prior to entry she had begun to have cerebral symptoms. There was a definite change in judgment and memory. She had a responsible job, and from being a very efficient person she became relatively inefficient, forgetting things and showing evidence of poor judgment.

DR BAUER: She also was fatigued and complained of being tired going upstairs. Dr Ropes elicited that information from the nurse and secretary some time after admission. The blood pressure never did rise. The highest recorded is 170, and some time later it was only 140 or 150.

DR KRANES: A fairly normal blood pressure during the development of renal insufficiency is evidence against the diagnosis of glomerulonephritis. As I have just stated, what disturbs me more than either the absence of casts or the elevation of blood pressure is the fever and peripheral discomfort that she had. Fever, of course, is not an uncommon ac-

DR MEANS'S DIAGNOSIS

Carcinoma of thyroid gland?
Chronic thyroiditis, Hashimoto type?

ANATOMICAL DIAGNOSES

Chronic thyroiditis, Hashimoto type
Hyperplasia of thyroid gland

PATHOLOGICAL DISCUSSION

DR CASTLEMAN I am sorry that Dr Cope is not here. He operated on the patient and first exposed some lymph nodes that were grayish white and slightly firm, but he did not believe they were neoplastic and at operation he favored chronic thyroiditis. The isthmus of the pyramidal lobe and part of the left lobe were excised and they also appeared grayish white. We performed a frozen section on the thyroid gland and found no neoplasia but a Hashimoto struma, and I will show the sections from it. This is the low-power view showing a uniform infiltration with lymphoid germinal centers throughout the thyroid gland. Of particular interest is the condition of the acini, which are definitely hyperplastic. The epithelium is high, and there is scalloping of the colloid, which is quite common in hyperplasia. It is not unusual to find actual hyperplasia in the early stages of Hashimoto struma. One theory of the pathogenesis of Hashimoto struma is that it is really a burned-out hyperthyroidism, this may be an early stage. Ordinarily patients with this disease are women between forty and fifty years of age, in these cases we may not see as much germinal center formation but more of a diffuse lymphocytic infiltration, with compression and replacement of colloid acini, which may give rise to a low basal metabolic rate and myxedematous signs and symptoms.

DR MEANS Another possible explanation would be compensatory hyperplasia due to the fact that the infiltrative process had destroyed the rest of the parenchyma. The remnant became hyperplastic to take care of the function. In the older patient did you find any areas of hyperplastic parenchyma?

DR CASTLEMAN Not usually. The older patient tends to develop myxedema.

DR MEANS That is when all the parenchyma is knocked out, and there is nothing left to become hyperplastic. That was another point in differential diagnosis between cancer and chronic thyroiditis. If one can prove that there is hypothyroidism, it is real evidence in favor of chronic inflammation rather than cancer, because cancer, no matter how diffuse, rarely knocks out the parenchyma completely with resulting myxedema.

DR CASTLEMAN This patient did not have a basal metabolic rate before operation. One month

following operation a basal metabolic rate is recorded as -4 per cent.

DR ALLAN M BUTLER Do you endorse the diagnostic biopsy, Dr Means?

DR MEANS Yes

CASE 35162

PRESENTATION OF CASE

A forty-nine-year-old woman was admitted to the hospital because of joint and muscle pains.

Two weeks prior to admission the patient developed a sudden sharp pain in the right anterior thigh that extended down to the knee. Two days later a similar pain developed in the left anterior thigh and sacroiliac region. Aspirin seemed to relieve most of the pain, but she took as much as 0.6 gm (10 gr) four or five times a day. Several days before entry she stopped the medication because of the development of ringing in the ears and nausea. Four days prior to admission both calves became stiff and tender, and the temperature rose to 101°F. Two days before entry a swelling, redness, some pain and tenderness occurred over the left internal malleolus, and a similar swelling occurred on the right heel on the day before admission.

There was no history of previous joint or muscle pains. She was said to be sensitive to house dust. She denied ever having taken sulfonamides.

Physical examination revealed a fairly comfortable woman, with a warm, moist skin. There was a blotchy, erythematous rash about the elbows, left wrist (1 to 3 cm in diameter) and the left internal malleolus. These areas were not indurated or elevated. There was a soft, Grade II systolic murmur at the apex. There was slight bilateral calf tenderness and a soreness of the heels.

The temperature was 103°F, the pulse 120, and the respirations 24. The blood pressure was 120 systolic, 68 diastolic.

Examination of the blood disclosed a hemoglobin of 14.6 gm and a white-cell count of 13,200, with 70 per cent neutrophils, 27 per cent lymphocytes, 2 per cent monocytes and 1 per cent basophils. Frequent band forms were seen. The platelets appeared normal. The urine gave a +++ test for albumin, with a specific gravity of 1.022, and the sediment contained as many as 20 red blood cells and 25 white blood cells per high-power field.

Sulfadiazine therapy was begun on admission. The erythematous blotches on the skin appeared to come and go from hour to hour. On the second hospital day 2000 cc of dextrose in physiologic saline solution and 200 cc of sodium lactate were given. The urinary output decreased to 250 cc on this day, and simultaneously the patient appeared to go into acute cardiac decompensation. Digitalis and other measures were required. The temperature continued to remain elevated up to 102°F, and on the third

cases that clinically seemed to have one disease and pathologically the other

Finally, I think one other disease should be mentioned, although it is pretty far-fetched. I am sure those who saw the patient will think it absurd. But as I get the picture from the description in the record of the initial symptoms in her legs — pain, stiffness of the calf and tenderness, the possibility occurred to me that the patient had an acute thrombophlebitis, although nothing further is said about it. If that were so, one might easily conceive of this process extending up into the iliac veins, possibly to the vena cava, and if it extended up far enough, it might occlude the mouths of both renal veins or extend into the renal veins causing hemorrhagic infarction of both kidneys and renal insufficiency. I realize it is a rare and unusual possibility but, as the picture is given here, not an impossible one.

In summary, then, I think we have to consider only three general possibilities: glomerulonephritis, one of the lesions produced by sulfonamides and periarteritis nodosa. Of these three possibilities it seems to me that the least objectionable one would be periarteritis nodosa. So I shall guess that that was what this patient had.

DR TRACY B MALLORY: I take it that the x-ray films are not contributory?

DR STANLEY M WYMAN: No, there is just a question of pleural reaction at the left, which may perhaps tend to implicate the pleura rather than the pericardium. Whether that is a help, I do not know.

DR KRANES: I do not see how it casts any light on the renal problem.

DR BAUER: The following note shows what we thought about this woman at the time of entry and what we believed she might be suffering from, although we would be the first to admit that we were not too certain of the exact nature of the disease (this was written six days after admission).

When I first saw this patient I thought she was suffering from meningococemia manifested by fever, headache, rash and arthritis. Sulfadiazine was started on the same day (3 gm). After a total of 7 gm of sulfadiazine, oliguria was evident, although there was no history of previous ingestion of any type of sulfonamide. On the same day she received 2200 cc. of physiologic saline solution as well as two ampules of sodium racemic lactate. This added sodium intake was sufficient to increase the patient's blood volume to a point where obvious signs of congestive failure

appeared. With the discontinuance of sulfadiazine, penicillin (400,000 units every twenty-four hours) therapy was instituted. Forty-eight hours after the start of sulfadiazine and twenty-four hours after penicillin the temperature fell, and the leukocyte count dropped from 13,000 to 6000. Up to today I felt reasonably certain that the patient had had a bacterial infection that had responded to specific treatment, but that she had the misfortune of developing a sulfonamide nephrosis and congestive failure by increasing her blood volume at a time when she had oliguria. The oliguria has improved, and the patient is now able to take fluids much better.

This morning the clinical picture resembles that seen on the day of entry, except that the rash is not as marked and the vesicular lesions on the chest are pruritic. Could the reappearance of these findings be related to the barbiturate she received last night? Is she sensitive to other agents than sulfonamides? For the time being it seems unwise to use any type of sedative.

At the moment I am unable to make a satisfactory diagnosis. I am still inclined to believe we have been dealing with a patient who had a bacterial infection, who is sensitive to sulfonamides and perhaps other drugs. There is little to suggest either rheumatic fever or rheumatoid arthritis. We must still entertain the possibility of subacute bacterial endocarditis, lupus erythematosus and periarteritis nodosa. Treatment for the time being should be good nursing and a minimum of drugs.

Subsequent to that Dr Ropes obtained additional information that the patient had not been feeling well for at least six months. Frankly, I must say that up to the time she died I did not know for certain what she was suffering from, but was inclined to believe it was more likely periarteritis nodosa or lupus erythematosus disseminatus. The last we heard from the Pathology Department they were not certain, but perhaps we will see.

CLINICAL DIAGNOSES

Periarteritis nodosa
Uremia

DR KRANES'S DIAGNOSIS

Periarteritis nodosa

ANATOMICAL DIAGNOSES

Lower-nephron nephrosis
Pericarditis, acute
Myocarditis, focal
Pneumonitis, interstitial
Bronchopneumonia, terminal
Hematopoiesis of spleen

PATHOLOGICAL DISCUSSION

DR MALLORY: The Pathology Department is far from certain about this case. We are able to name

companionment of glomerulonephritis, but fever of this degree and muscle and joint pains of this degree are not common symptoms of glomerulonephritis

Dr Bauer is showing me the chart, which indicates fever in the beginning, gradually coming down to normal. Perhaps the glomerulonephritis, if present, was a complication of some other acute infectious process. What that may have been, I certainly have no idea. There is no evidence on which to localize any type of acute infection. To be sure, during the latter part of the illness she developed a pericardial friction rub, but I am interpreting that as the type of fibrinous pericarditis that so often develops in the terminal stages of uremia. The swelling over the parotid area was a terminal, purulent parotitis in all probability. Whether she had subacute bacterial endocarditis and a complicating nephritis as a result is difficult to say. I am not able, on the evidence given here, to make a diagnosis of subacute bacterial endocarditis.

The presence of fever, pain and renal disease raises the question of acute pyelonephritis. The urinary sediment is not very helpful in establishing such a diagnosis. If this were pyelonephritis, one would have to assume that there was pre-existing renal disease. An acute attack would not be expected to produce death so rapidly.

We come now to a discussion of the possible role of sulfonamides in this patient's terminal illness. I would like to ask how certain we can be that she received no sulfonamides before coming to the hospital.

DR ROPES I am very sure that she had not received any.

DR KRANES That is important because there is some evidence on admission to the hospital that this patient already had renal disease as evidenced by the albuminuria and the hematuria. The picture as described indicates that sulfonamides may have played some role in the development of the subsequent renal insufficiency, since the urinary output seems to have diminished following their administration. If the history is accurate, and we have to believe it is, I do not see how we can incriminate the sulfonamides as underlying this renal disease. They may have aggravated it.

The usual types of lesions produced by sulfonamides, as you know, are precipitation in the renal tubules of sulfonamide crystals and the rapid development of oliguria. That is a possibility. Another

type of lesion is lower-nephron nephrosis, which, unless this patient had previously been given sulfonamides, seems improbable. The third type of lesion produced by sulfonamides is a periarterial lesion, periarteritis nodosa, first described by Rich* and subsequently confirmed by other workers on clinical cases. On the whole, I would be inclined to disregard the role of sulfonamides in this particular patient, since she had renal disease before they were given.

We know that periarteritis can exist in the absence of sulfonamide administration. It is a disease that has to be seriously considered in this patient. I see nothing in the history as given here that would be against such a diagnosis. The muscular and joint pains, the fever and the renal disease all fit that diagnosis. One thing that bothers me about such an explanation is the short course of this patient's illness. Dr Ropes has added further data indicating that this patient had not been in good health for six months. That would fit in very well with the diagnosis of periarteritis. Of course, all the features of the disease were not present here. There was no eosinophilia, but that is not too disturbing. There was no asthma.

In this regard I think it might be worth speculating about the possible role of sulfonamides, if this patient does turn out to have had periarteritis nodosa. I do not believe Dr Mallory will be able to answer that, but it is interesting to speculate about it. Given a patient with periarteritis nodosa, what would happen if sulfonamides were given, a drug we know is capable of producing the disease in a sensitized patient? I do not know. It does seem from the description that the disease might have been accelerated by the administration of sulfonamides, but I do not see how we can answer the question.

What I have said about periarteritis applies equally well to another disease — acute disseminated lupus. The differential between the two I do not believe I can make clinically. When I say "periarteritis nodosa" I mean that the patient might also have had the renal lesions of disseminated lupus, although pathologically they are quite different. The skin rash, joint pains and fever and even the pericardial friction rub, although it is much more likely to have been a uremic pericarditis, might have been evidences of disseminated lupus. We have seen

*Rich A. R. Role of hypersensitivity in periarteritis nodosa as indicated by 7 cases developing during serum sickness and sulfonamide therapy. *Bull. Johns Hopkins Hosp.* 71:123-140, 1942.

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"I HAVE CANCER"

AS ALREADY noted in these columns, April is the month in which interest in the control of cancer is brought to its sharpest focus. Consideration has been given to heart-disease month, and the nation is currently passing through cancer-control month, mindful of the 1949 goal of \$14,500,000 in donations to be achieved, according to a recently developed national tradition, the country is in fact encountering a succession of chronological periods especially consecrated to unusually worthy causes.

Of the hazards to life that mankind is now constantly combating with better equipment and with greater success than ever before, heart disease and cancer offer a significant comparison. Each is ac-

knowledgeed as particularly important among the diseases of later life, each, in certain aspects, being evidence of the inevitable wearing out of the human machine. Each is of increasing importance as a cause of death, largely because of the considerable control that has been acquired over the diseases of early life.

Here, however, the similarity ends. Degenerative diseases of the heart are accepted almost as a badge of merit. They are considered to be the penalty of industrious application to one's duty and the discharging of a personal debt to society, with interest. Like ulcer, they represent a wound stripe of modern civilization. Cancer, ominous and mysterious, inspires a terror that the conception of heart disease seems to lack. It still implies a portentous degree of finality, as if the knell were already struck, the tolling of the bell begun.

The reasons for these differences in viewpoint are obvious. Heart disease warns of its encroachment on the patient's health, and good behavior may postpone indefinitely the final accounting. The idea of a fighting chance for the prolongation of life, with reasonable activity and comfort, is almost always present. Cancer, on the other hand, is a fifth column that may have infiltrated beyond hope of eradication before it is discovered. The medical profession itself, with the label of "malignancy" that it has applied to cancer, has helped to emphasize the horror associated with it.

No enemy can be hopefully opposed that is allowed to entrench itself in the shadows. Implicit in the campaign against cancer is the bringing of it into the open. The lesson must be reaffirmed that cancer is a disease that can be combated and frequently conquered if early diagnosis is permitted. Many new agents both of diagnosis and of treatment are being brought to bear against it. Reticence is one of its most powerful allies.

The *Reader's Digest* for November, 1948, contains an article by a newspaper editor, entitled "I Have Cancer." The point of this courageous story, by one whose condition was apparently discovered too late for successful treatment, is that "the paralyzing hush hush that surrounds cancer" must be dispelled. In the interest of early diagnosis with its increased

the renal lesion, for what that is worth. She had a severe lower-nephron nephrosis, with pigment casts in many of the distal tubules and the usual degenerative changes in the ascending limbs of Henle's loops, the interstitial inflammation and thrombi of the large renal veins, which are all characteristic of this lesion. Beyond that we are in the realm of pure speculation. We found a fibrinous pericarditis. Microscopically, there was an extensive, focal myocarditis and also interstitial pneumonitis. There were a few granulomatous lesions in the portal areas of the liver. A complete surprise, since there was nothing to suggest a blood dyscrasia, was the presence of many foci of hematopoiesis in the spleen. The bone marrow was very hyperplastic in both red-cell and white-cell series. There was acute arteritis and phlebitis in a small tab of mesenteric fat in one of the epiploic appendices, but no other vascular lesions elsewhere in the body. The joints were normal, as were the heart valves. None of the lesions in the heart were characteristic of Aschoff bodies or other stigmas of rheumatic fever. We found nothing to substantiate a diagnosis of rheumatic fever, rheumatoid arthritis, lupus erythematosus or periarteritis nodosa. This type of case makes one think very seriously of the possibility of some of the rare infections — histoplasmosis or toxoplasmosis — but a number of us in the laboratory have searched the sections repeatedly and are unable to find any organisms of such character.

I am also unable to explain the development of the lower-nephron nephrosis in this case. I agree with

Dr. Kranes that the history strongly suggests that the patient had renal disease before she had sulfonamides, and I do not believe we can attribute the lesion to sulfonamide therapy. The possibility that the lesion develops following the sensitization to other drugs has been raised on a few occasions. I have seen a case in which it was attributed to streptomycin, though on flimsy evidence. I have never heard of it following aspirin, which is the only drug mentioned in the immediate past history.

DR. BAUER: In retrospect, I wish we had never given sulfonamides because the sequence of events that ensued following the administration of the sulfonamides was perhaps coincidental but, nevertheless, very impressive. Would you agree to that, Dr. Ropes?

DR. ROPES: Yes, it was very impressive.

DR. BAUER: If I had to do it again, I would never have employed sulfonamides. The patient's brother was a physician, her sister was a teacher and very intelligent, and on more than one occasion we tried hard to get a history from them of the previous taking of sulfonamides but could not. Whether that rules out sulfonamide sensitivity, I do not know.

DR. JACOB LERMAN: It seems to me that it is easy to get sensitivity to sulfonamides by the use of ointments and nose drops that almost every doctor gives in his practice every day.

DR. MALLORY: Yes, there was one case that, as far as we could make out, was sensitized by a sulfonamide chewing gum.

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POTASSIUM IODIDE AND STREPTOMYCIN FOR TUBERCULOSIS

Most of the clinical experience with the streptomycin treatment of pulmonary tuberculosis has indicated that this antibiotic is effective against the acute exudative lesions and that little or no benefit may be expected in the chronic fibroid or fibrocaseous types of pulmonary lesions, in which the antibiotic may not have adequate access to the organism. In an attempt to create experimentally a more favorable opportunity for streptomycin to act on such lesions Woody and Avery¹ have utilized the well known clinical observation that the administration of iodides causes tubercle bacilli to appear in the sputum of patients with pulmonary tuberculosis in whom the organisms were previously absent.

The rationale for their experiments is based upon the observations of Jobling and Petersen² that iodides may act on the tuberculous lesion in two ways: it may combine with the unsaturated fatty acids of the tubercle bacilli and neutralize their ferment-inhibiting properties, the enzymatic action that then occurs within the areas of caseation liberates the bacilli from these foci. In addition, the iodides facilitate the solution and absorption of the caseous material, thus exposing the bacilli that might otherwise be inaccessible to the agents.

After determining that potassium iodide has no effect on the antibiotic properties of streptomycin, Woody and Avery set up controlled experiments in guinea pigs to determine whether potassium iodide in combination with streptomycin would be more effective than streptomycin alone against a virulent tuberculous infection. The early results seem to justify their expectation. In their first experiment, treatment was started three weeks after infection, and all animals were killed seven weeks after infection. The control animals and those receiving only potassium iodide all showed heavy tuberculous in-

fection, some of the animals treated with streptomycin alone demonstrated a spread of infection to the organs during treatment while the organs of the animals treated with the combination of potassium iodide and streptomycin were entirely free of infection on gross examination. In a second experiment in which animals were observed for fifteen weeks after infection, all the control animals died, 6 of 13 streptomycin-treated animals died, whereas only 2 of 14 given streptomycin and potassium iodide died.

These results seemed impressive enough to stimulate clinical trials of this type of therapy, which are now in progress. It should be borne in mind, however, that the treatment is not without some risk. If potassium iodide causes a breakdown of the tuberculous lesion and if streptomycin treatment results in the rapid appearance of streptomycin-resistant organisms, as is usually the case, one defense of the body has been eliminated. In some of the patients in whom the resistant organisms appear, the lesions may then be expected to progress more rapidly after this treatment, and streptomycin may then be without effect and potentially harmful.

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"HONOUR A PHYSICIAN"

A SPECIAL convocation was held on Sunday afternoon, January 23, at Hobart and William Smith Colleges to mark the one hundredth anniversary of the graduation from Geneva (now Hobart) College of Elizabeth Blackwell, the first woman to receive a degree in medicine. Ten leading women physicians from the United States and Canada and one each from England and France were cited by Dr. Alan W. Brown, president of the Geneva Colleges, in the name of Elizabeth Blackwell, the response was by Dr. Priscilla White, of Boston.

New England received its share of the honors of the day, for of the ten American and Canadian physicians selected by the deans of the medical schools of the two countries, four are natives of New England.

Dr Martha May Eliot, associate chief of the United States Children's Bureau, is also the first woman to have been president of the American Public Health Association. A native of Dorchester, Massachusetts, she graduated from Johns Hopkins University School of Medicine in 1918.

Dr Alice H. Hamilton, of Hadlyme, Connecticut, professor emeritus of Industrial Medicine at Harvard, was the first woman to be a member of the Harvard faculty. A graduate of the University of Michigan Medical School in 1893, she was cited for her contributions to industrial toxicology.

Dr Helen B. Taussig, born in Cambridge, Massachusetts, received her degree in medicine at Johns Hopkins University School of Medicine, where she is now associate professor of pediatrics. She is the winner of many awards for her work with Dr Alfred Blalock in studying and developing operative techniques for the correction of congenital cardiac defects.

Dr Priscilla White, a graduate in 1923 of Tufts College Medical School, is a clinical teacher at that school, a practicing physician in Boston and a member of the staff of the New England Deaconess Hospital. She is, in the words of Dr Brown, "known throughout the land for her research in the field of diabetes with special reference to diabetic children and mothers. Representing here today the women doctors of the world, we are proud to cite her for her own service to medicine and medical research."

The *Journal* takes pride also in honoring these four women, and with them their illustrious colleagues. Dr Florence R. Sabin, of Denver, Colorado, Dr Gerty T. Cori, of Webster Groves, Missouri, Dr Helen V. McLean, of Chicago, Illinois, Dr Margaret D. Craighill, of Topeka, Kansas, Dr Helen MacMurchy, of Toronto, Canada, Dr Elise S. L'Esperance, of New York, Dr Helen M. Mackay of London, England, and Dr Thérèse Bertrand Fontaine, of Paris, France.

TRANSCUTANEOUS JET PROPULSION

THOSE Americans have invented a new gadget, described first by Hingson and Hughes¹ in 1947, employed by Hirsh and his co-workers² in 1948 and commented on not unfavorably, although with cau-

tion, in a recent issue of the *British Medical Journal*.³ It consists of a machine that can propel, painlessly and at a speed perhaps only slightly faster than sound a therapeutic or immunizing substance into, through and beyond the apparently unbroken epidermis.

The damvankees, long considered technical masters of the subject, have discovered a new way of getting under people's skin.

The Microjet or Hypospray is based on the principle that a fine, high-pressure jet can pierce the skin, with little if any pain. In its practical application, the material to be injected is placed in a metal ampule (or Metapule) with a capacity of 0.25 cc. The Metapule, shaped like a blunt-nosed bullet, has an orifice 0.003 inches in diameter in the rounded tip. The butt end is stoppered with a rubber plug, the Metapule is locked into the front end of the machine, and, when all is ready, a high-tension spring attached to a plunger is released by pressure on a button.

When this occurs "The plunger explodes against this rubber stopper which forces the material out of the Metapule and through the skin as a fine spray. The material is deposited subcutaneously and intramuscularly to depths varying from 0.2 to 2 cm depending on the tension of the spring and the site of injection." The jet exerts a pressure of 2300 to 3500 pounds per square inch on the skin, "which has no alternative but to let it through."

Hingson and Hughes find that blood concentrations of penicillin obtained with the Hypospray are higher and more prolonged than when needle and syringe are used, probably because parts of the solution are deposited subcutaneously as well as intramuscularly.

The warning is issued that a frontal attack must be made against the taut skin. If the skin is wet or the nose of the ampule is not in close contact with it or is tilted, the injection produces a cut or a blister.

This instrument is said to eliminate the fear incident to injection by needle and syringe.

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The rationale for their experiments is based upon the observations of Jobling and Petersen² that iodides may act on the tuberculous lesion in two ways: it may combine with the unsaturated fatty acids of the tubercle bacilli and neutralize their ferment-inhibiting properties, the enzymatic action that then occurs within the areas of caseation liberates the bacilli from these foci. In addition, the iodides facilitate the solution and absorption of the caseous material, thus exposing the bacilli that might otherwise be inaccessible to the agents.

After determining that potassium iodide has no effect on the antibiotic properties of streptomycin, Woody and Avery set up controlled experiments in guinea pigs to determine whether potassium iodide in combination with streptomycin would be more effective than streptomycin alone against a virulent tuberculous infection. The early results seem to justify their expectation. In their first experiment, treatment was started three weeks after infection, and all animals were killed seven weeks after infection. The control animals and those receiving only potassium iodide all showed heavy tuberculous in-

fection, some of the animals treated with streptomycin alone demonstrated a spread of infection to the organs during treatment while the organs of the animals treated with the combination of potassium iodide and streptomycin were entirely free of infection on gross examination. In a second experiment in which animals were observed for fifteen weeks after infection, all the control animals died, 6 of 13 streptomycin-treated animals died, whereas only 2 of 14 given streptomycin and potassium iodide died.

These results seemed impressive enough to stimulate clinical trials of this type of therapy, which are now in progress. It should be borne in mind, however, that the treatment is not without some risk. If potassium iodide causes a breakdown of the tuberculous lesion and if streptomycin treatment results in the rapid appearance of streptomycin-resistant organisms, as is usually the case, one defense of the body has been eliminated. In some of the patients in whom the resistant organisms appear, the lesions may then be expected to progress more rapidly after this treatment, and streptomycin may then be without effect and potentially harmful.

REFERENCES

1. Woody E. Jr. and Avery R. C. Combined effect of potassium iodide and streptomycin on established tuberculosis in guinea pigs. *Science* 108: 501, 1948.
2. Jobling J. W. and Petersen, W. Study of ferments and ferment-inhibiting substances in tuberculous caseous material. Studies on ferment action. XII. *J. Exper. Med.* 19: 383-397, 1914.

"HONOUR A PHYSICIAN"

A SPECIAL convocation was held on Sunday afternoon, January 23, at Hobart and William Smith Colleges to mark the one hundredth anniversary of the graduation from Geneva (now Hobart) College of Elizabeth Blackwell, the first woman to receive a degree in medicine. Ten leading women physicians from the United States and Canada and one each from England and France were cited by Dr. Alan W. Brown, president of the Geneva Colleges, in the name of Elizabeth Blackwell, the response was by Dr. Priscilla White, of Boston.

New England received its share of the honors of the day, for of the ten American and Canadian physicians selected by the deans of the medical schools of the two countries, four are natives of New England.

SIGNIFICANT FIGURES

To the Editor It should be of interest to all the readers of the *Journal*, including the proponents of compulsory health insurance, to know about the recent results of a poll taken of the members of the Worcester District Medical Society. The results of this poll, incidentally, were printed in the *Secretary's Letter* (of the American Medical Association), No 99, March 14, 1949.

In response to the poll in which they were asked to answer whether they were in favor of or opposed to compulsory health insurance as proposed by Senate Bill S 5, 75 per cent of the members took the time to answer—a remarkable number of returns, particularly when doctors are concerned. Ninety-seven per cent were opposed to compulsory health insurance, and only three per cent were in favor of it. Out of 330 returns, 313 were opposed, 11 were in favor and 1 was undecided.

This should be the answer for those who use the word "many" with no facts or figures to back it up. When the minority groups make a statement that many doctors favor Government medicine, they should be shown that when transposed into percentages, 3 per cent looks a lot less than the word many.

N S SCARCELLO, *Chairman*
Public Relations Committee
Worcester District Medical Society

Worcester, Massachusetts

REGARDING GROUP PRACTICE

To the Editor The title of the fine editorial in support of Senator Chapman's Local Public Health Units Act of 1949 (S 522), which appeared in the February 24 issue of the *Journal*, caught my eye because of my interest in still "another bulwark against socialized medicine"—that is, prepaid group practice.

In 1947 Hunt and Goldstein, in the *New England Journal of Medicine* (237 71-77 and 719-731, 1947) and in the *Journal of the American Medical Association* (135-904-909, 1947, and 136 857-861, 1948), reviewed the services, organization, administration and professional opinion of 368 group-practice plans. Eight of the 368 were in New England, and 2 were in Massachusetts. None of the 8 were on a prepaid basis.

In May, 1948, the representatives of the American Medical Association at the National Health Assembly in Washington agreed "that voluntary prepayment group health plans offer to their members the best of modern medical care" and that "the people have the right to establish voluntary insurance plans on a co-operative basis." The more recent twelve-point program, as pointed out in the *Journal of the American Medical Association* (139 529, 1949), implies accession to these principles.

At the Massachusetts Health Conference held last month in Boston, the panel on medical-care costs and methods reaffirmed the advantages of group-practice prepayment plans, and encouraged their use, as noted in the editorial entitled "Massachusetts Five-Year Plan" in the March 10 issue of the *New England Journal of Medicine*. However, debate was largely between the proponents of the two extreme points of view—that is, improved coverage within the *status quo* and national health insurance. Consequently, the acknowledged best compromise measure yet proposed received little attention.

The response of communities that have been in urgent need of improved medical care and have also been afforded friendly and encouraging legislation and professional co-operation confirms the practical applicability of such plans. Since Texas passed its Rural Co-operative Health Plan bill in 1945, 50 consumer-sponsored medical-plan charters have been granted and 17 hospital clinics have been established. In Wisconsin enabling legislation enacted July, 1947, has been followed by at least 5 co-operative plans and a co-operative hospital opened in Wild Rose, Wisconsin, little more than a year later.

The American Medical Association argues that a broad federal health program at present is premature in the face of the lack of sound experience and experimentation. It has voiced its readiness to accept the types of medical service plans that, although voluntary, can afford the experience needed to provide better medical care at a minimum cost to

medically marginal communities. Those communities may be either sparsely settled areas or of marginal income populations. In either case, given the opportunity, many communities are ready and eager to experiment in this field of medical economics.

An American Medical Association questionnaire of doctors in the armed services indicated that 54 per cent preferred group practice. All, of course, had been experiencing a sort of prepaid group practice while in the service. It seems reasonable that these two groups, doctors and consumer patients, might with encouragement from national and local medical associations get together on a mutually satisfactory basis.

Therefore, it is to be hoped that some of the progressive steps outlined in the twelve-point program will be furthered by the active support of organized medicine in the removal of restrictive legislation and its positive encouragement of participation by doctors in voluntary medical-care plans of all types compatible with high standards of medical science and ethics.

DONVILL W BOARDMAN, M.D.

Maynard, Massachusetts

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

An Index of Treatment By various writers. Edited by Sir Robert Hutchison, Bt., M.D., LL.D., F.R.C.P., consulting physician London Hospital and Hospital for Sick Children, Great Ormond Street. Assisted by Reginald Hilton, M.A., M.D., F.R.C.P., physician to St. Thomas's Hospital, consulting physician, Epsom Hospital, and consulting physician and cardiologist, Wembley Hospital. Thirteenth edition, revised 4th, cloth, 972 pp., with 99 illustrations. Baltimore: Williams and Wilkins Company, 1948. \$17.00.

This treatise was first published in 1907, and this edition has been thoroughly revised, and the subject matter brought up to date. The text is the joint work of seventy-four contributors. The material is arranged alphabetically, and there is a supplemental comprehensive index of sixty pages. The type and paper are good, and a light paper is used to advantage in such a large volume. The number of editions speaks well for the soundness of the work, and it should prove valuable to the practicing physician and is recommended for all medical libraries as a standard reference work.

Urology for Nurses. By Oswald S. Lowsley, M.D., director, Department of Urology (James Buchanan Brady Foundation), New York Hospital, consulting urologist, St. Clare's Hospital and Hospital for the Ruptured and Crippled, New York City, Monmouth Memorial Hospital, Long Branch, New Jersey, Englewood Hospital, Englewood, New Jersey, St. Luke's Hospital, Newburgh, New York, St. Agnes Hospital, White Plains, New York, and Norwalk Hospital, Norwalk, Connecticut, and Thomas J. Kirwin, M.D., attending surgeon, Department of Urology (James Buchanan Brady Foundation), New York Hospital, visiting genitourinary surgeon, New York City Hospital, consulting urologist, Conec Island Hospital, Monmouth Memorial Hospital, Long Branch, New Jersey, Benedictine Hospital, Kingston, New York, and St. Vincent's Hospital, Montclair, New Jersey. Second edition. 8th, cloth, 637 pp., with 130 illustrations by William P. Didusch. Philadelphia: J. B. Lippincott Company, 1948. \$6.00.

The authors have revised this second edition of their manual for nurses, first published in 1936, to bring it up to date. Some chapters have been completely rewritten, and cystoscopy and radiography have been brought together in one chapter. Many illustrations have been added. A glossary of urologic terms and a good index conclude the text. The book is well published and should prove useful as a compendium of the subject.

MASSACHUSETTS MEDICAL SOCIETY POSTGRADUATE LECTURE COURSE

The April 25 session of the Postgraduate Lecture Course will be held in the New Lecture Hall, Cambridge, instead of at Sanders Theater

The New Lecture Hall is located across Kirkland Street from Sanders Theater, at the corner of Kirkland and Oxford streets

A M.A. ASSESSMENT

The following letter will, I am sure, interest many fellows of the Society

H Quimby Gallupe, M D
8 Fenway
Boston 15, Massachusetts

Dear Dr Gallupe

Enclosed is my check for special assessment.

I am impressed with the sincerity and efforts of the Society officers to meet the issues squarely. I also feel that the critical efforts through the town meetings of doctors has been effective in guiding the efforts that reached Chicago through our local organization.

From here on it is up to the younger members of the American Medical Association to attend the district meetings and see that constructive proposals are carried upward through our organization.

Sincerely yours,

EARLE M. CHAPMAN, M D

H QUIMBY GALLUPE, *Secretary*

DEATHS

BAILEY — Florence Bailey, M D, of Lawrence, died on December 24. She was in her seventy-second year.

Dr Bailey received her degree from College of Physicians and Surgeons, Boston, in 1903.

CRITTENDEN — Samuel W. Crittenden, M D, of Wakefield, died on March 27. He was in his ninety-third year.

Dr Crittenden received his degree from Dartmouth Medical School in 1898. He was a member of the New England Society of Psychiatry.

His widow survives.

HUGHES — John Hughes, M D, of Pittsfield, died on February 12. He was in his sixty-seventh year.

Dr Hughes received his degree from University of Vermont College of Medicine in 1905. He was associate medical examiner of Berkshire District and was a member of the staffs of St Luke's and Pittsfield General hospitals. He was a former councilor of the Massachusetts Medical Society.

His widow, two daughters, five grandchildren and his mother survive.

WARREN — Hobart E. Warren, M D, of Palm Beach, Florida, died on March 17. He was in his eighty-first year.

Dr Warren received his degree from Harvard Medical School in 1894. He was a former member of the Massachusetts Medical Society and a fellow of the American Medical Association.

His widow and a daughter survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The May schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

CLINIC	DATE	CONSULTANT
Salem	May 2	Paul W. Hugenberger
Haverhill	May 4	William T. Green
Lowell	May 6	Albert H. Brewster
Greenfield	May 9	Charles L. Sturdevant
Gardner	May 10	Carter R. Rowe
Brockton	May 12	George W. Van Gorder
Springfield	May 17	Garry deN. Hough, Jr.
Pittsfield	May 18	Frank A. Slowick
Worcester	May 20	John W. O'Meara
Fall River	May 23	David S. Grace
Hyannis	May 26	Paul L. Norton

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

MISCELLANY

INFANT MORTALITY, 1947

The infant mortality rate in 1947 was the lowest recorded in the United States, according to a release from the National Office of Vital Statistics of the Public Health Service, Federal Security Agency. The rate in that year fell from the 1946 figure of 33.8 infant deaths per thousand live births, to 32.2. It was expected that the decline would continue to a rate of 31.8 in 1948.

The five leading causes of infant deaths in 1947 and the rates for each are: premature birth, 11.1; congenital malformation, 4.6; pneumonia and influenza, 3.6; birth injury, 3.5; and asphyxia and atelectasis, 1.6.

CORRESPONDENCE

MORE ON THE CARE OF THE PATIENT

To the Editor: I fully agree with Dr. Henry F. Howe's letter, "The Care of the Sick" in the March 10 issue of the *Journal*. I should, however, like to add a word of advice, and it is this: every medical graduate should have, besides an internship, an externship. Every physician, when he first starts out to practice for himself, knows the clumsy and embarrassing situations he frequently finds himself in. He lacks bedside manners; he does not have the proper approach toward either the patient or his immediate family. He is unable to advise on home nursing care — (as an intern he seldom, if ever, had to make such decisions). The general practitioner, not infrequently, has to use his resourcefulness in improvising gadgets that the intern has no need for. No lectures, books or films can make one adept in doing things, and only by actually doing things can one learn to do them well. To solve these as well as many more unforeseen problems that arise, I suggest that every young physician, after completing his internship, should be apprenticed for a year to a busy country general practitioner. The actual practical experience thus obtained would benefit not only the patient, but much more so the physician beginner. He would acquire the skill in diagnosing correctly the largest number of his cases without having to resort to the so-called instruments of precision (most of them are not) and would thus save precious time. In a word, he would develop the self-confidence that goes to make a good physician.

MOSES ABIV, M D

Ellenville, New York

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TREATMENT OF MENTAL ILLNESS AT HOME BY SMALL DOSES OF INSULIN

A Follow-up Report and Appraisal of Results in Twenty-Six Cases

NEWMAN COHEN, M D *

BOSTON

THE belief that treatment of mental illness requires a hospital setting is no longer uniformly accepted. The extramural approach has been strengthened substantially by an increasing number of favorable reports.

Electroshock therapy, formerly used only in hospitalized patients, has been used successfully in ambulatory patients.¹⁻⁶ Today it is possible, in many cases, to administer this type of treatment outside the hospital, thus obviating loss of time and any stigma connected with hospitalization in a mental institution. However, such a procedure is recommended only in carefully selected cases and with adequate safeguards.

Insulin-coma therapy as a potent therapeutic agent in schizophrenia has been recognized.⁷⁻⁸ This treatment is drastic, however, and usually requires a hospital setting for proper administration.

There is a large group of patients who do not require hospitalization and whose mental condition lends itself to insulin sub-shock treatment carried out in the patient's home. Personal results with this latter form of therapy have been reported in a previous presentation,⁹ which contained short-term data in 12 cases treated with this method. The treatment has subsequently been continued, and the number of cases now totals 26. The purpose of this paper is to present a follow-up report of the previous cases and our clinical observations on the cases subsequently treated by insulin sub-shock in the home.

The use of modified insulin-coma therapy as a method of management in mental disorders was long overshadowed by the more drastic therapies and received scant attention and application.

The first reference to the therapeutic use of mild hypoglycemic shock was that of Cowe.¹⁰ In a previous paper,⁹ the important pertinent literature was summarized. There have been other workers who have directed attention to the value of sub-coma insulin.¹¹⁻¹⁵ In an evaluation of the "shock" therapies in 1945 Bennett¹⁶ mentioned the value of sub-coma doses of insulin as a method of sedation, to control

the patient's anxiety and excitement and to permit a better psychotherapeutic approach. Rennie²⁰ carried out the insulin sub-shock method of treatment on a group of 28 heterogeneous patients and described striking results with marked clinical improvement in 19 cases. Dramatic relief was achieved with insulin in excitement whenever anxiety prevailed. Rennie found that insulin sedation was superior to sedation by ordinary chemical methods. Insulin therapy permitted a marked degree of relaxation, enabled the patients to discuss their pre-occupations and provided a real opportunity to utilize psychotherapy.

Kalinowsky and Hoch²¹ observed that patients with anxiety states were more amenable to psychotherapy when treated with sub-coma doses of insulin. Disturbances in the autonomic nervous system quieted down under insulin, the patient had a better appetite, slept better and gained in weight.

Beneficial results with sub-coma insulin have been reported in the treatment of acute alcoholism.²²⁻²³

Hohman and Kline²⁴ used insulin sub-coma on 37 patients with anxiety states, depression and psychosomatic disturbances. The results indicated that this method of therapy was valuable, effective and safe in a variety of anxiety states, particularly those arising in the military service in men with combat experiences. Almost all the patients treated showed some degree of improvement, and many of the responses were dramatic.

Kelley and Thompson²⁵ also described favorable results in a report in 5000 patients treated by the method described by Sargant and Slater.²⁶

Sullivan,²⁷ summarizing his experiences in 393 cases (324 psychoses and 69 psychoneuroses), concluded that intensive sub-shock therapy was of value in all relatively acute psychoses with schizophrenic symptoms. Rapid clinical improvement was achieved in the psychoneurotic patients. These studies indicated that all patients with psychoneurotic states of the severe anxiety-tension type, all psychoses with schizophrenic symptoms, psychoses with feelings of depression and psychoses of mixed type

* Psychiatric consultant, Rehabilitation Board, Veterans Administration physician. Out Patient Department, Boston State Hospital.

Principles Governing Eye Operating Room Procedures By Emma I. Clevenger, R.N., supervisor, eye operating room, New York Eye and Ear Infirmary, New York City 8^o, cloth, 215 pp., illustrated St. Louis C. V. Mosby Company, 1948 \$5.50

This manual outlines the procedures for the operating room of an eye hospital. It discusses the care and handling of instruments and equipment, sutures, dressings, rubber gloves, linens and drugs. A large part of the book is devoted to a description of setups for various eye operations. It is based on experience gained in the New York Eye and Ear Infirmary. The books should prove useful to eye surgeons and hospital libraries.

"Elective Alimentary Rest" and the Elimination of So-called "Paralytic Ileus" after Abdominal Operations By V. J. Kinsella, M.B., Ch.M. (Sydney), F.R.C.S. 8^o, paper, 35 pp., with illustrations Sydney, Australia Australasian Medical Publishing Company, Limited, 1948 3 shillings

This pamphlet brings together a number of papers originally published in periodicals by the author. The author describes his postoperative plan, especially in cases of appendicitis, in which no solids or solid-forming liquids are given for six days after the operation. A diet for the six days is given, consisting of liquids, except milk, and soft foods. Aperients, enemas, hypodermic injections for retention of urine and drugs, such as pituitrin and eserine, are not permitted. The author claims excellent results for his treatment based on 344 cases of acute appendicitis treated during a period of twelve years.

General Endocrinology By C. Donnell Turner, Ph.D., associate professor of zoology, Northwestern University 8^o, cloth, 604 pp., with 163 illustrations Philadelphia W. B. Saunders Company, 1948 \$6.75

This textbook is designed for beginning students who are concentrating on experimental biology and is based on the lectures given at Northwestern University. The subject is approached from the experimental rather than the clinical point of view. The material is well organized and bibliographies are appended to the various chapters. A good index concludes the volume. The publishing is excellent. The book is recommended for all medical libraries and to all students interested in the subject.

NOTICES

ANNOUNCEMENT

Dr. George P. Sanborn announces that he has resumed the practice of medicine at Hotel Elton, 370 Commonwealth Avenue, Boston.

HAMPDEN DISTRICT MEDICAL SOCIETY

The annual meeting of the Hampden District Medical Society will be held at the Longmeadow Country Club, Tuesday, April 26, and not at the Highland Hotel as formerly announced.

Cocktails will be served at 6:00 p.m.

The speaker of the evening will be Dr. Douglas T. Davidson whose subject will be "Convulsive Disorders."

94TH INFANTRY DIVISION LECTURES

The 94th (Bay State) Infantry Division is sponsoring a series of monthly lectures by prominent physicians in their respective specialties. The third lecture will be held in Room 720, United States Post Office and Court House, Post Office Square, Boston, on Wednesday, April 27, at 8 p.m.

Dr. Morton Brown will speak on the subject "Physiologic Approach to Congestive Heart Failure."

All interested physicians, whether reserve officers or not, are cordially invited to attend this carefully planned program. Reserve officers will be given one point credit. Excellent films will also be shown during this period.

NEW ENGLAND HEART ASSOCIATION

The annual Henry Jackson Lecture, under the auspices of the New England Heart Association, will be given by Dr. Harold G. Wolff, professor of medicine and associate professor of psychiatry, Cornell University Medical College, and attending physician, New York Hospital, at the Boston Medical Library, 8 Fenway, Boston, on Monday, May 9, at 8:15 p.m. His subject will be "Life Stress and Cardiovascular Disorders."

A short business meeting will precede the lecture. Interested physicians and medical students are invited to attend.

AMERICAN PSYCHIATRIC ASSOCIATION

The one hundred and fifth annual meeting of the American Psychiatric Association will be held at the Windsor Hotel, Montreal, Quebec, May 23-27.

The question of the reorganization of the Association, which has been under consideration for several years, will come up for further discussion at this meeting, and an unusually large attendance is expected.

SOCIETY MEETINGS AND CONFERENCES

APRIL 23 Massachusetts Association of Medical Technologists. Page 628 issue of April 14

APRIL 26 Greater Boston Medical Society. Page xv issue of April 14

APRIL 26 Hampden District Medical Society. Notice above

APRIL 27 94th Infantry Division Lectures. Notice above

APRIL 28 Massachusetts Psychiatric Society and Boston Society of Psychiatry and Neurology. Page xv issue of April 14

APRIL 30 Long Island College Alumni Association. Page 528 issue of March 31

MAY 2-26 Consultation Clinics for Crippled Children in Massachusetts. Page 666

MAY 4 New England Obstetrical and Gynecological Society. Springfield Country Club Springfield

MAY 5 Suffolk Censors Meeting. Page 276 issue of February 17

MAY 5 Roswell Park Lecture and Medal. Page 588 issue of April 7

MAY 7 New England Society of Anesthesiologists. Page 401 issue of March 10

MAY 9 New England Heart Association. Notice above

MAY 10 Harvard Medical Society. Lower Out Patient Department Amphitheater Massachusetts General Hospital

MAY 12 Chemotherapy of Leukemia and Lymphosarcoma. Dr. William Dameshek. Pentucket Association of Physicians. 8:30 p.m. Haverhill

MAY 16-19 American Urological Association. Biltmore Hotel Los Angeles California

MAY 18-21 Association for Physical and Mental Rehabilitation. Page 401 issue of March 10

MAY 23-27 American Psychiatric Association. Notice above

MAY 24-26 Massachusetts Medical Society. Annual Meeting Worcester Memorial Auditorium Worcester

MAY 24-26 Massachusetts Physicians Art Association. Page 588 issue of April 7

MAY 26-28 American Gout Association. Hotel Lorraine Madison, Wisconsin

MAY 30-JUNE 3 International Congress on Rheumatic Diseases. Page 800 issue of November 18

JUNE 1-3 Academy of Neurology. Page 588 issue of April 7

JUNE 2-5 American College of Chest Physicians. Page 490 issue of March 24

JUNE 3-5 Christian Medical Society. Page xv issue of April 14

JUNE 20-23 Annual Conference of Health Officers and Public Health Nurses. Page xvii issue of February 3

JUNE 20-23 American Society of Medical Technologists. Page 574 issue of March 31

JUNE 30-JULY 2 American Association of Railway Surgeons. Page 490 issue of March 24

SEPTEMBER 6-10 American Congress of Physical Medicine. Page xiii issue of March 24

SEPTEMBER 28-30 Mississippi Valley Medical Society. Page 1060 issue of December 30

OCTOBER 8-15 American Society of Clinical Pathology. Page xiii issue of March 24

NOVEMBER 2 New England Obstetrical and Gynecological Society. Hotel Somerset Boston

DISTRICT MEDICAL SOCIETIES

HAMPDEN

APRIL 26, 6:00 p.m. Longmeadow Country Club Springfield (Dinner Meeting) Convulsive Disorders. Dr. Douglas T. Davidson

(Notices concluded on page xi)

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* Psychiatric consultant, Rehabilitation Board, Veterans Administration Physician, Out Patient Department, Boston State Hospital.

should receive intensive insulin sub-shock therapy Noyes²⁸ and Smith and Branch²⁹ agree in essence with this view and point out that sub-coma doses of insulin are useful as a means of sedation to control anxiety, to improve physical health and to make a more favorable psychotherapeutic approach possible

Psychotherapy has generally been employed as a routine procedure in conjunction with sub-coma insulin therapy for its important value in consolidating the clinical gains and maintaining improvement. A number of published reports have described the effective use of combinations of therapies. Among these is the work of Gottesfeld and Novaes,¹⁶ who described gain in weight in 2 cases of anorexia nervosa treated with sub-shock insulin and narcoanalysis

Stratton et al¹⁷ reported 60 consecutive cases in which the treatment featured psychotherapy as facilitated by combined sub-coma insulin and pentothal narcosis. The results were as follows: good recovery in 63 per cent, fair in 23 per cent, mild in 10 per cent and poor in 3 per cent

In 1944 Weil and Moriarty¹³ explored the therapeutic possibilities of a course of insulin treatment in a group of 20 patients with schizophrenic reaction types who had responded poorly to electroshock treatment alone. Insulin was administered either according to Sakel's method or with sub-coma doses. Fifty per cent of these patients responded promptly to insulin. (Sub-shock doses of insulin produced satisfactory results in 4 of the present series of cases.) In 4 patients the authors tried a second course of electric shock after a rest period, with disappointing results

In a more recent study Polatin and Spotnitz³⁰ attempted to determine whether rapid clinical improvement achieved with electroconvulsive therapy in schizophrenia could be maintained or enhanced by supplementary sub-coma insulin treatment. Thirty female patients with schizophrenia were treated with this procedure over a period ranging from ten to forty-two weeks. Improvement was noted in 80 per cent of the patients treated by this method over a period of thirteen weeks. It was generally found that best results were achieved if insulin treatment was employed after the sixth electric shock. After the sixth electroconvulsion, the two therapies were administered concurrently, electroshock treatment being given three times weekly. The authors believed that this method combined the rapid beneficial effects of electroshocks with the slowly cumulative favorable effects of mild daily hypoglycemic shocks

Sullivan²⁷ utilized the combined therapeutic approach but reversed the procedure. A group of patients with hebephrenic schizophrenia, manic states and atypical depressive states with elements of schizophrenia who failed to benefit from insulin therapy were subsequently given a course of electro-

shock treatments. The patients with manic states responded fairly well to subsequent electroshock. According to the author this method increases the over-all rate of improvement and remission to 90 per cent in patients with psychoses who do not respond satisfactorily to intensive insulin sub-shock therapy. He found that when electroshock was administered before insulin therapy, the patients who showed symptoms of depression and schizophrenia usually lost the symptoms of depression but retained those of schizophrenia. Since the schizophrenic symptoms are considered more malignant, the importance of relieving these symptoms as soon as possible was pointed out, any remaining significant degree of depression could be treated with electroshock

MANAGEMENT AND TECHNIC

The treatment^{20, 21, 24, 27, 30} should be carried out by a physician who has had training in neuropsychiatry as well as the shock technics. The initial handling of the patient's fears is frequently a project in itself, and psychotherapy is utilized in helping him accept the treatment. The attitude of the patient does not materially lessen the effectiveness of insulin sub-shock therapy, but lack of co-operation tends to create an awkward situation and is a definite drawback should subsequent psychotherapy be required. The physician should obtain the written consent of the patient's family before proceeding with the treatment

Each patient to be treated is given a preliminary physical survey. This includes a general physical and neurologic examination, a roentgenologic study of the chest and an electrocardiogram. In addition to a carefully taken history and examination of the mental status, a urinalysis and blood chemical studies are done prior to treatment. Contraindications include metabolic disturbances, acute and chronic liver and kidney disease, active pulmonary tuberculosis and myocardial damage. Age alone should not be a reason for withholding this form of therapy. As a rule, a patient in relatively good health is suitable for treatment, since the physical risks with the sub-coma insulin method are usually minimal. In view of the possibility of complications, the physician must be in attendance and must observe the patient closely during the entire period of active treatment. Moreover, the physician should be easy of access for the remainder of the day in the event that the hypoglycemic state returns

The possibility of hypersensitivity to insulin should not be overlooked. The occurrence of erythema, edema, pruritus, urticaria, tachycardia, nausea and vomiting has been described in persons treated with insulin. Insulin sub-shock as a method of management has been relatively free of complications, although such untoward insulin effects as convulsions were described in 35 out of 332 cases

by Sullivan,²⁷ who reported a fatal case in a twenty-two-year-old soldier in excellent physical condition, who had been acutely psychotic for about three months. On the fifth day of treatment he suddenly went into full shock about twenty minutes after receiving a dose of 60 units. He died three days later without regaining consciousness.²⁷ Deaths resulting from the use of small doses of insulin were also described in sub-shock treatment of a case of schizophrenia and in tonic treatment of a case of delirium tremens.³¹ The clinical and patho-anatomic features in these two cases were identical with those observed in fatal complications of ordinary insulin shock therapy.

Insulin sub-coma is similar to the first phase of insulin shock treatment. The basic principle of this method is to inject insulin and after a variable period to terminate the hypoglycemic state by the administration of glucose and food. Efforts are directed toward stabilizing the dose of insulin and avoiding the occurrence of actual hypoglycemic coma. The site of the injection should be changed frequently to avoid local tissue irritation and necrosis. The patient, having fasted for from four to twelve hours, is given insulin by deep intramuscular injection of 5 to 15 units. The dose of insulin may be increased by about 10 units daily until mild hypoglycemic shock, manifested by lassitude, increased perspiration, hunger, thirst and somnolence, is produced. The dosage is then kept at a minimal level and shock reactions are avoided by feeding. The amount of insulin required to produce a state of hypoglycemia varies with the individual patient. Usually 50 to 100 units of insulin is sufficient to cause appearance of the desired hypoglycemic manifestations in about an hour. The patient is kept in a state of hypoglycemia for periods ranging from thirty to ninety minutes, and the reaction is then terminated by the administration of sugared fruit juice followed by a meal rich in carbohydrates. If treatment has to be interrupted early, the dosage should be decreased on the following day by 5 to 10 units. Weakness and clamminess after treatment generally indicate incomplete termination. In the mild hypoglycemic state the patient is usually able to take sugared fruit juice orally. Fluids should not be forced if the patient has difficulty in swallowing. Interruption of the hypoglycemia on such occasions is best carried out by the intravenous injection of 20 cc of a sterile 33.3 per cent glucose solution. This is usually effective in arousing the patient to the point where he will be able to drink.

After termination of treatment the clothing should be changed because of the increased perspiration that has occurred, and chilling of the patient is avoided. Most patients are routinely encouraged to exercise a few hours after treatment. They are routinely instructed to carry candy bars for use at the first sign of hypoglycemic symptoms. They are also encouraged to eat as much food as possible during the

remainder of the day. Insulin treatment is carried out six times a week with one day's rest. Duration of treatment is determined by therapeutic progress. As a rule, acute states require less time than chronic ones. Generally, treatment is indicated as long as the patient continues to show improvement. Patients should be observed for one month after completion of therapy, which should be resumed at once in the event of relapse.

THERAPEUTIC RESULTS

This report describes a group of 26 heterogeneous cases treated over a three-year period and includes several patients with schizophrenia of many years' standing who showed the usual clinical features of withdrawal, apathy, projection and negativism. Because of the prominent role that insulin occupies in mental disorders and because of the growing recognition of the possibilities of sub-coma insulin treatment, it is believed that some of the clinical observations and data merit attention. Sufficient time has elapsed for the over-all results in the original series of 12 cases to be more accurately appraised, and the increased number of cases treated with the ambulatory method permits more valid deductions concerning the applicability and effectiveness of this management. By and large, the progress of both groups of patients treated has been encouraging and gratifying.

Table 1 contains follow-up summaries of the cases previously reported in which insulin sub-shock treatment was given at home from January, 1945, to February, 1946. Table 2 presents a summary of data and short-term follow-up information of a group of patients subsequently treated during 1946 and 1947. A few of the patients have had follow-up examinations for periods up to two years.

The results in the 26 cases were as follows: all but 1 of the patients treated showed definite clinical improvement of varying degrees. In Group I, 7 out of 12 patients made complete recoveries and have remained well. One patient recovered and subsequently relapsed to a moderate degree. She has remained in a much improved state after a short course of electroshock therapy. This patient refused the full course of treatment, since she felt entirely well and preferred to spend the summer at the beach. One patient, who relapsed fourteen months after termination of treatment, was subsequently treated by narcoanalysis and electric shock and has continued to maintain a much improved state. Two patients who improved moderately discontinued treatment prematurely, but have maintained their clinical gains. One patient was much improved, and his clinical improvement has continued to date.

In Group II, 10 out of 14 patients made complete recoveries. One patient, a schizophrenic of many years' standing in whom an organic brain defect was suspected, made a slight clinical improvement, but subsequently relapsed and regressed. One patient

should receive intensive insulin sub-shock therapy Noyes²⁸ and Smith and Branch²⁹ agree in essence with this view and point out that sub-coma doses of insulin are useful as a means of sedation to control anxiety, to improve physical health and to make a more favorable psychotherapeutic approach possible

Psychotherapy has generally been employed as a routine procedure in conjunction with sub-coma insulin therapy for its important value in consolidating the clinical gains and maintaining improvement. A number of published reports have described the effective use of combinations of therapies. Among these is the work of Gottesfeld and Novaes,¹⁵ who described gain in weight in 2 cases of anorexia nervosa treated with sub-shock insulin and narcoanalysis

Stratton et al¹⁷ reported 60 consecutive cases in which the treatment featured psychotherapy as facilitated by combined sub-coma insulin and pentothal narcosis. The results were as follows: good recovery in 63 per cent, fair in 23 per cent, mild in 10 per cent and poor in 3 per cent

In 1944 Weil and Moriarty¹³ explored the therapeutic possibilities of a course of insulin treatment in a group of 20 patients with schizophrenic reaction types who had responded poorly to electroshock treatment alone. Insulin was administered either according to Sakel's method or with sub-coma doses. Fifty per cent of these patients responded promptly to insulin. (Sub-shock doses of insulin produced satisfactory results in 4 of the present series of cases.) In 4 patients the authors tried a second course of electric shock after a rest period, with disappointing results

In a more recent study Polatin and Spotnitz³⁰ attempted to determine whether rapid clinical improvement achieved with electroconvulsive therapy in schizophrenia could be maintained or enhanced by supplementary sub-coma insulin treatment. Thirty female patients with schizophrenia were treated with this procedure over a period ranging from ten to forty-two weeks. Improvement was noted in 80 per cent of the patients treated by this method over a period of thirteen weeks. It was generally found that best results were achieved if insulin treatment was employed after the sixth electric shock. After the sixth electroconvulsion, the two therapies were administered concurrently, electroshock treatment being given three times weekly. The authors believed that this method combined the rapid beneficial effects of electroshocks with the slowly cumulative favorable effects of mild daily hypoglycemic shocks

Sullivan²⁷ utilized the combined therapeutic approach but reversed the procedure. A group of patients with hebephrenic schizophrenia, manic states and atypical depressive states with elements of schizophrenia who failed to benefit from insulin therapy were subsequently given a course of electro-

shock treatments. The patients with manic states responded fairly well to subsequent electroshock. According to the author this method increases the over-all rate of improvement and remission to 90 per cent in patients with psychoses who do not respond satisfactorily to intensive insulin sub-shock therapy. He found that when electroshock was administered before insulin therapy, the patients who showed symptoms of depression and schizophrenia usually lost the symptoms of depression but retained those of schizophrenia. Since the schizophrenic symptoms are considered more malignant, the importance of relieving these symptoms as soon as possible was pointed out, any remaining significant degree of depression could be treated with electroshock

MANAGEMENT AND TECHNIC

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Each patient to be treated is given a preliminary physical survey. This includes a general physical and neurologic examination, a roentgenologic study of the chest and an electrocardiogram. In addition to a carefully taken history and examination of the mental status, a urinalysis and blood chemical studies are done prior to treatment. Contraindications include metabolic disturbances, acute and chronic liver and kidney disease, active pulmonary tuberculosis and myocardial damage. Age alone should not be a reason for withholding this form of therapy. As a rule, a patient in relatively good health is suitable for treatment, since the physical risks with the sub-coma insulin method are usually minimal. In view of the possibility of complications, the physician must be in attendance and must observe the patient closely during the entire period of active treatment. Moreover, the physician should be easy of access for the remainder of the day in the event that the hypoglycemic state returns

The possibility of hypersensitivity to insulin should not be overlooked. The occurrence of erythema, edema, pruritus, urticaria, tachycardia, nausea and vomiting has been described in persons treated with insulin. Insulin sub-shock as a method of management has been relatively free of complications, although such untoward insulin effects as convulsions were described in 35 out of 332 cases

excess and was domineering, selfish, abusive and assaultive. Thwarted in her attempt at separation or relief and faced with continued marital discord and stress, the patient sank into a deep depression marked by thoughts of suicide.

At a hospital a course of electroshock treatment brought partial relief for 5 months, but in September, 1946, the patient relapsed. Various forms of medical management as well as psychotherapy proved ineffective. Examination revealed a brow-beaten, preoccupied, depressed, resentful and discour-

been more harmonious, irritation and frustration have been minimal, and she has remained well for 20 months after termination of treatment.

CASE 14 A 48-year-old single man had shown mental symptoms for 10 years prior to hospitalization in September, 1939. While at the hospital he had been dull, disinterested and emotionally blunted. As time went on he continued to be evasive, suspicious and paranoid in his trends. Although he

TABLE 2 Results in 14 Patients Treated with Insulin Sub-Shock at Home

CASE No.	AGE	SEX	DURATION OF ILLNESS BEFORE AMBULATORY TREATMENT	CLINICAL PICTURE	PREVIOUS TREATMENT	DURATION OF SUB-COMA INSULIN TREATMENT	CLINICAL RESPONSE	FOLLOW-UP DATA
13*	40	F	2½ yr	Depressive psychosis	Electroshock therapy psychotherapy	19 wk.	Recovery	Patient entirely well at follow-up examination 1½ yr later
14*	48	M	17 yr	Schizophrenia, paranoia	Insulin and metrazol shock series	11 wk.	Improvement to a degree relapse.	Follow-up examination 2 yr later revealed further clinical regression
15*	25	F	9 mo.	Schizophrenic reaction with paranoid trends and depressive features	Electroshock therapy	19 wk.	Much improvement after 9 wk. of treatment relapse recovery after additional 10 wk. of treatment.	Complete clinical recovery after 19 wk. of treatment patient entirely well at follow-up examination 15 mo. later
16*	29	F	3 yr	Obsessive-compulsive state with emotional inadequacy and instability and depressive features	Medical management	18 wk.	Recovery	Patient entirely well at follow-up examination 1½ yr after termination of treatment
17*	40	M	3 yr	Schizophrenia acute catatonic reaction state.	Electroshock therapy	20 wk.	Recovery after 16 wk. of treatment slight relapse followed by recovery	Recovery followed by slight relapse 4 mo. later maintenance treatment employed for 4 wk. followed by recovery patient entirely well at follow-up examination 2 yr 1 mo. later
18	60	F	5 yr	Reactive depression somatization reaction with emotional instability and hypochondriasis.	Operations on gall bladder uterus and hemorrhoids medical management.	5 wk.	Much improvement patient refused full course of treatment home conditions unsuitable for insulin sub-shock treatment.	Patient showed considerable improvement despite unsuitable treatment setting at follow-up examination 1½ yr later clinical gain maintained, but patient showed lack of enthusiasm for improved condition.
19	34	F	8 yr	Schizophrenic reaction	Electroshock therapy relapse 1 mo. later	10 wk.	Fluctuating improvement poor co-operation relapse soon after interruption of treatment.	Patient's family unable to cope with situation treatment discontinued prematurely with subsequent relapse.
20	34	M	9 mo	Anxiety and tension	Medical management excessive barbiturates	12 wk.	Recovery	Recovery had persisted at follow-up examination 1 yr., 1 mo. after termination of treatment
21	26	F	14 mo	Schizophrenic reaction	Electroshock therapy	17 wk.	Recovery	Recovery had persisted at follow-up examination 1 yr., 5 mo. after termination of treatment
22	33	F	2 yr	Anxiety and tension with depressive and compulsive features	Medical management	11 wk.	Recovery	Patient entirely well at follow-up examination 2 yr later
23	27	F	1½ yr	Schizophrenia, paranoid type	Electroshock therapy	10 wk.	Much improvement relapse.	Patient refused full course of treatment and maintained improvement for 1 yr and then relapsed
24	36	M	14 yr	Recurrent depressions	Three courses of electroshock therapy	14 wk.	Much improvement	Improvement continued steadily until complete recovery patient entirely well at follow-up examination 1½ yr after termination of treatment.
25	33	F	3 yr	Manic-depressive reaction type	Two courses of electroshock therapy with subsequent relapse	16 wk.	Recovery	Complete recovery maintained at follow-up examination 11 mo. later
26	23	M	6 mo	Anxiety and tension with depressive features	Medical management psychotherapy barbiturates in large amounts.	9 wk.	Recovery	Patient entirely well at follow-up examination 1½ yr after termination of treatment

*Cases reported in text.

aged woman. Her symptoms included anxiety, tension, insomnia, crying spells and many somatic complaints.

Insulin sub-shock therapy was begun in the patient's home in December, 1946. After 5 weeks of treatment there was a general remission of symptoms. The treatment was continued for 19 weeks, the maximum dose of insulin being 150 units. The patient became more accessible to psychotherapy. Her depression lifted, fear, anxiety and tension abated, and a happier and more satisfactory domestic relationship was effected.

She resumed her social activities and derived considerable pleasure and satisfaction out of life. The home situation has

denied hallucinations, there was evidence that he reacted to them at intervals. In 1944 family placement in the community was tried but he had to be returned because of poor adjustment. A full course of insulin and metrazol shock treatments brought partial improvement, but he soon relapsed into his former self-absorbed, seclusive state. He constantly refused to occupy himself in any way and, his appetite having been exceptionally good, he tended to be rather obese. A diagnosis of schizophrenia, paranoid type, was made but there had been considerable deterioration intellectually and emotionally during the rather prolonged course of his mental illness. He was not considered suitable

showed much clinical improvement, but progress was hampered by situational factors. Despite premature interruption of treatment, the clinical gains have been sustained. In 2 other cases, treatment was insufficient, and the clinical improvement was ultimately followed by relapse.

Of the 26 patients treated, 17 were restored to their pre-morbid state and were entirely free of any

In most cases insulin sub-shock therapy produced remarkable improvement in physical condition. The patients frequently gained weight rapidly and developed a feeling of well-being. Another attractive feature of the treatment was that they became more amenable to psychotherapy. Abnormal states marked by fear, doubt, inhibition and misconceptions were often relieved. The rapidity with which

TABLE 1 *Results in 12 Patients Previously Reported**

CASE No	AGE	SEX	DURATION OF ILLNESS BEFORE AMBULATORY TREATMENT	CLINICAL PICTURE	PREVIOUS TREATMENT	DURATION OF SUB-COMA INSULIN TREATMENT	CLINICAL RESPONSE	FOLLOW UP DATA
1	28	M	15 mo	Anxiety and tension	Barbiturates medical management	11 wk.	Recovery	Patient entirely well at follow-up examination 2½ yr later
2	30	F	12 mo	Depressive psychosis	None	12 wk.	Recovery	Recovery had persisted at follow-up examination 2 yr 7 mo later
3	40	F	4 yr	Anxiety and tension emotional instability	Barbiturates psychoanalysis electroshock therapy	10 wk.	Recovery relapse	Slight relapse 1 yr and 3 mo after termination of treatment patient eventually treated with electric shock and has remained much improved for past 13 mo.
4	56	M	17 mo	Depressive features	Endocrines opiates psychotherapy electroshock therapy	8 mo	Recovery	Patient entirely well at follow-up examination 1½ yr later
5	37	F	2 wk.	Schizophrenic reaction	Medical management	18 wk.	Recovery	Recovery had persisted at follow-up examination 2 yr, 1 mo later
6	26	M	10 mo	Depressive reaction emotional instability somatization reaction	Psychotherapy vitamins sedatives	11 wk.	Recovery	Patient entirely well at follow-up examination 3 yr 2 mo after termination of treatment
7	42	F	14 yr	Anorexia nervosa emotional instability anxiety and tension	Psychotherapy medical management	4½ mo	Recovery	Recovery maintained at follow-up examination 3½ yr later
8	40	F	2 yr 7 mo	Anxiety and tension phobias emotional instability somatic disturbances	Electroshock therapy psychotherapy narcoanalysis	4 mo	Recovery	Patient has remained entirely well 3 yr after termination of treatment gave birth to her first child several months ago
9	46	F	1½ yr	Anorexia nervosa anxiety and tension	Barbiturates in excessive amounts	10 wk.	Moderate clinical improvement weight gain (12 lb)	Patient refused full course of treatment returned to former weight level follow-up examination 3 yr later revealed unsatisfactory home situation weight has remained stationary no clinical regression
10	47	M	3½ yr	Depressive reaction emotional instability	Barbiturates health resorts osteopathic treatment psychotherapy medical management	18 wk.	Much improvement, slight relapse	Clinical improvement maintained for 14 mo aided by supplementary narcoanalysis on 3 occasions patient eventually relapsed slightly and received short course of electroshock therapy has continued much improved since then
11	38	F	6 yr	Neurotic personality emotional instability somatization reaction weight loss	Barbiturates	9 wk.	Much improvement weight gain (12 lb)	Patient refused full course of treatment and returned to previous clinical state follow-up examination conducted 1 yr 11 mo after discontinuance of treatment disclosed no subsequent weight loss or clinical regression
12	23	M	5 yr	Emotional instability immaturity inadequacy somatization reaction	Psychotherapy	10 wk.	Much improvement gain in weight personality improvement	Clinical gains sustained at follow-up examination 1½ yr after termination of treatment spirits have remained elevated improvement in attitude of confidence and poise social and economic adjustment has remained relatively normal

manifest residual symptoms at follow-up examinations conducted at periods ranging from eleven months to three years and four months after completion of treatment. Premature interruption of treatment appeared to influence the clinical results in 6 cases. Two patients relapsed but subsequently improved with electroshock therapy. Only 2 patients relapsed and regressed.

symptoms of anxiety and tension diminished was often striking.

CASE REPORTS

In the interest of brevity only 5 illustrative cases are reported. They include 4 recoveries and 1 failure.

CASE 13. A 40-year-old married woman first developed symptoms of depression in May, 1944. Her husband drank to

Insulin sub-shock therapy is a less drastic procedure than insulin shock and in all probability produces no irreversible brain damage (Patients given as many as a hundred or more sub-coma treatments showed no evidence of mental deterioration)

Patients are spared the atmosphere of a hospital, with its locked doors and barred windows

The treatment is relatively economical, because therapy is administered at home and hospitalization is not necessary

Complications occur less frequently than with the more drastic forms of therapy^{27 31}

The treatment is not incapacitating, and the patient is usually able to be up and about promptly. This has two important advantages over other methods: the patient is more amenable to psychotherapy, and he is alert and able to join in activities immediately

Insulin sub-coma greatly relieves anxiety and tension and is often a better sedative than barbiturates^{9 24 27}. The effects are more incisive and lasting than those with chemical sedation,²⁰ which often increases anxiety rather than relieves it. An additional drawback to the use of chemical sedation, especially barbiturates, is the danger of intoxication

Insulin sub-shock treatment improves the patient's physical condition

Another reason favoring ambulatory treatment is advanced by Impastato et al.³ "Since the ambulatory patient gets well while at home, there is no need for subsequent home readjustment [which] must be achieved by the hospital patient at the end of treatment"

Supplementary treatment in the event of a relapse is often not feasible after the patient has left the hospital. In the ambulatory method there is usually no difficulty in maintaining post-treatment supervision, promptly resuming treatment or in administering occasional subsequent treatment

DISADVANTAGES

In general, the disadvantages of the ambulatory method of management are outweighed by its social and various other advantages

A natural disadvantage is the time factor, several hours of the physician's attention usually being required.⁹ There has been a tendency on the part of some therapists toward impatience with slower methods of treatment, and a preference for more rapid and less demanding procedures

The disadvantages of ambulatory treatment described by Fetterman³ are readily applicable to the method of therapy discussed above. They include the following

Increased responsibility on the part of the family — the patient may require help in eating

and guidance in activity. Those entrusted with the patient's safety must carry out such responsibilities zealously

The initial improvement may prompt the desire for premature discontinuance of treatment — a contingency that can usually be handled quite adequately in hospital treatment

The hazard of suicide is of paramount importance and may present a serious problem to home management of the patient. In cases in which the urge to self-destruction is overwhelming, or in which the patient's welfare or that of society is endangered, he should be hospitalized. The suicide hazard in ambulatory treatment can be minimized by careful selection of patients, by early treatment and by constant vigilance on the part of the family

Home treatment is hazardous and probably contraindicated if there is a clash of personalities in the home situation or if there is lack of understanding of the clinical problems

SUMMARY

Twenty-six patients treated with the insulin sub-coma method at home are described. Daily treatments were administered for periods ranging from two to eight months. All but 1 of the patients showed definite clinical improvement of varying degrees. Seventeen patients were restored to their pre-morbid state and were free of residual symptoms

Sub-coma insulin therapy is a relatively safe procedure and can be administered at home

The advantages and disadvantages of this type of therapy, the technic of administration and the necessary precautions to safeguard the patient are outlined

Several case histories are presented

In view of the favorable results achieved and the many advantages offered, further use of sub-coma insulin therapy in the patient's home appears justified

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21 Bay State Road

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for leukotomy because of the absence of depression, anxiety and agitation

Through the efforts of his family, his release from the hospital was obtained. Despite the rather gloomy prognosis, insulin sub-shock treatment was undertaken at home in deference to the wishes of his family.

Daily treatment with sub-coma doses of insulin was begun on September 13, 1946. The clinical response was almost immediate. The patient became more spontaneous, rational and co-operative. His outlook became more objective, and his emotional response more adequate, and after 3 weeks of treatment he managed to work part time as a truck-driver's helper.

However, memory impairment, which had been quite pronounced, failed to improve, and an organic process was suspected. An x-ray film of the skull taken on October 22 was normal. An electroencephalogram was obtained on October 24, with findings consistent with organic brain damage.

Toward the end of November it was noted that he failed to make further improvement and had begun to regress. Carelessness in his personal habits, shallow affective responses and obsessive-compulsive features became prominent, and interest in work waned. The patient had received 11 weeks of treatment with no significant clinical change, the maximum dose of insulin being 90 units. Treatment was discontinued, and he returned to the hospital.

At follow-up examination 2 years later, he had regressed further. He displayed a marked memory defect, lack of interest, apathy and seclusiveness.

CASE 15 A 25-year-old overprotected single woman with a history of several frustrating experiences suffered additional bitter disappointment when rejected by her fiancé on his return from overseas duty. Overwhelmed by this series of psychic traumas, she succumbed to a schizophrenic psychosis marked by depression, paranoid trends, emotional instability, preoccupation and withdrawal.

Electroshock treatment at a hospital brought temporary relief for 3 months, but in September, 1946, the patient relapsed. Despite attempts at medical management and psychotherapy, little headway was made. She gradually became more depressed, withdrawn and paranoid in her trends. Her family refused permission for electroshock therapy and frowned upon further hospitalization.

Insulin sub-coma treatment was begun at home in December. The first short period of improvement was noted in 3 weeks. Thereafter, intervals of well-being became more prolonged, and symptoms continued to diminish progressively. Psychotherapy was employed advantageously with the patient, who previously had not been readily accessible to such a procedure. These psychotherapeutic sessions proved of value in hastening the disappearance of abnormal functioning and in restoring insight. After 9 weeks of treatment she had gained 14 pounds in weight. The maximum dose of insulin was 110 units. She gradually became more objective, contented and stable and was considered recovered.

She relapsed mildly a month later, and treatment was immediately resumed and weighted in the direction of psychotherapy for a 10-week period. Improvement continued steadily until complete recovery.

This patient subsequently remained entirely well. She has continued in a state of recovery for 13 months since completion of treatment and during the greater part of that time has been gainfully employed as a dressmaker. She continues to be personable, ambitious and objective. In an interview recently with her family, the remark was made, "She has never been so well in her life."

CASE 16 A 29-year-old woman, the product of a broken home, was emotionally labile, basically dependent and intellectually inadequate. Her husband, a laborer and of different faith, had an essentially similar personality profile. His overprotective mother was a constant source of friction in the household. As a result of the patient's basic shyness, limited educational and cultural background, she was unable to compete with others, and her social contacts were restricted. A childless marriage helped to make her life drab. There was marked disproportionate sex drive between husband and wife, and when future months left them childless, the patient began to blame herself and experienced feelings of guilt over past sexual indiscretions. Her history had been negative for preceding significant illnesses.

She began to have frequent crying spells, was intensely preoccupied and unable to sleep and began to mutter in a compulsive manner at frequent intervals, "I give my soul to the devil." Anxiety gradually increased, she suffered from anorexia, vomiting and frequent compulsive urges to run to the bathroom. She finally sank into a severe depression. Various types of medical management proved ineffective. The case was not suitable for psychotherapy. Her family refused to sanction hospitalization or electroshock therapy.

Insulin sub-shock therapy was begun at home 9 months after the onset of the illness. She was treated daily for 18 weeks. Her anxiety diminished after 3 weeks of treatment, and the symptoms began to abate. She gained considerable weight and became more cheerful, self-reliant and less preoccupied with feelings of guilt. She continued to improve, the obsessive-compulsive tendencies gradually disappeared, and the depression lifted completely. Even though her disorder was not suitable for psychotherapy, she improved steadily until complete recovery 18 weeks after the institution of treatment.

She subsequently remained somewhat timid, but her ability to mingle socially with others improved and she gradually developed new interests and lived more harmoniously with her husband. On follow-up examination 18 months later, she was entirely well and contented. Social and marital adjustment had continued to be satisfactory.

CASE 17 A 40-year-old Italian married man with an extremely unstable heredity and background, and with a history since 1942 of two separate psychotic episodes lasting approximately 8 weeks each, suffered an acute turmoil reaction in 1945.

A course of electroshock therapy and subsequent various forms of medical management brought some palliation, but in May, 1946, he succumbed to a fourth attack characterized by excitement, agitation, refusal of food and personal neglect and undue preoccupation with religion and the abstract, together with a compelling desire to become a crusader and reformer. Hallucinations and delusions were prominent. Aggressive behavior increased to ominous proportions. Hospitalization was not permitted largely because two of his brothers had already been hospitalized in a mental institution.

Insulin sub-shock therapy was begun at home at once. The clinical response was dramatic, and in approximately 2 weeks the excitement had subsided.

Gradually, there was a reduction and finally disappearance of confusion, hallucinations, paranoid ideas and feelings of unreality. Despite the rather recent psychotic manifestations, the patient was soon able to return to work. Anxiety disappeared completely even though he was unable to profit from psychotherapy. The treatment proved especially effective in controlling excitement and in checking hallucinations and delusions.

Improvement with further treatment was steadily progressive, and there was gradual abatement of all symptoms until complete recovery 20 weeks after the initiation of treatment. Except for a mild, brief relapse, treated by a few additional episodes of sub-coma, he has remained well for the 25-month follow-up period.

ADVANTAGES

Ambulatory insulin sub-coma is considered a preferred therapeutic measure in psychiatric disorders. The treatment has proved of value in a variety of mental conditions and in many cases that have been refractory to other methods of management. Some of the advantages over the more drastic forms of therapy were described in a previous article.⁹ These advantages as well as several others have a practical bearing and deserve emphasis. They include the following:

The treatment can be administered at home and thus obviates the stigma (in the mind of the patient and his relatives) of hospitalization.

Comparison of the Digitalis and Nondigitalis Groups

Type and dosage of digitalis At the time of appearance of bigeminy whole-leaf digitalis was being administered orally in 45 cases and digitoxin in 3. In 2 cases a mixture of digitalis glycosides (digalen) was given intramuscularly. The amount of digitalis given and the length of time during which the patient had received the medication before the appearance of bigeminy varied considerably. In most cases bigeminy appeared when the maintenance dose was increased, even in such small amounts as 0.05 to 0.1 gm. In 4 cases a profuse diuresis induced by parenteral administration of mercurial diuretics resulted in bigeminal rhythm without an increase in the maintenance dose of digitalis. In another case the same phenomenon was observed after a massive gastrointestinal hemorrhage.

Age and sex The average age of the patients in the digitalis group was 53.9 years, whereas in the

group, and auricular and sinus nodal extrasystolic bigeminy were almost as common (Table 4).

The features of the ventricular extrasystolic bigeminy in the two groups are shown in Table 5.

TABLE 2 *Etiologic Types of Heart Disease in Patients with Digitalis and Nondigitalis Bigeminy*

HEART DISEASE	DIGITALIS GROUP NO OF CASES	NONDIGITALIS GROUP NO OF CASES
None	0	19
Rheumatic	21	4
Rheumatic and hypertensive	4	0
Rheumatic and coronary	1	0
Hypertensive	4	15
Hypertensive and coronary	10	17
Coronary	6	21
Syphilitic	1	1
Calcereous aortic stenosis	1	1
Congenital	1	1
Indeterminate	1	3
Totals	50	82

Multifocal ventricular premature beats giving rise to bigeminy occurred only once in the nondigitalis group but were encountered 14 times in patients in the digitalis group. Ventricular premature beats arose in both ventricles in 8 cases of the digitalis

TABLE 1 *Age and Sex Distribution of 50 Patients with Digitalis and 82 with Nondigitalis Bigeminy*

AGE	DIGITALIS GROUP	NONDIGITALIS GROUP
0-10	0	5
11-20	0	0
21-30	6	2
31-40	2	7
41-50	10	8
51-60	15	21
61-70	12	27
71-80	4	13
81-90	1	1
Male	22	46
Female	28	36

nondigitalis group it was 56.7 years. There were no significant differences between the two groups in age and sex incidence (Table 1).

Heart disease Organic heart disease or essential hypertension was present in all the cases in the digitalis group and in 77 per cent of the control group. A wide variety of etiologic types of heart disease was encountered in both groups, but hypertensive and coronary-artery diseases were more common in the control group and rheumatic heart disease in the digitalis group (Table 2). With the exception of a case of auriculoventricular nodal rhythm, the basic cardiac rhythm was a normal sinus mechanism in all cases in the control group. In the digitalis group, on the other hand, the basic rhythm was a normal sinus mechanism in 28 cases, auricular fibrillation in 21, and auricular flutter in 1 (Table 3).

Electrocardiographic features In all cases but 2 the bigeminy in the digitalis group was due to ventricular extrasystoles. In contrast, ventricular extrasystolic bigeminy accounted for only 39 per cent of the cases of coupled rhythm in the nondigitalis

TABLE 3 *Basic Cardiac Rhythms of Patients with Digitalis and Nondigitalis Bigeminy*

RHYTHM	DIGITALIS GROUP NO OF CASES	NONDIGITALIS GROUP NO OF CASES
Normal sinus	28	81
Auricular fibrillation	21	0
Auricular flutter	1	0
Auriculoventricular nodal	0	1
Totals	50	82

group but not in a single case in the control group. On the other hand, basal ventricular premature contractions resulted in bigeminy in 10 cases in the nondigitalis group but not once in the digitalis group. The premature ventricular contractions of unifocal origin arose in either ventricle in both groups, but

TABLE 4 *Electrocardiographic Features in 50 Cases of Digitalis and 82 of Nondigitalis Bigeminy*

TYPE OF BIGEMINY	DIGITALIS GROUP	NONDIGITALIS GROUP
Sinus nodal extrasystolic	0	16
Auricular extrasystolic	1	29
Auriculoventricular nodal extrasystolic	1	3
Ventricular extrasystolic	46	32
Sinoauricular block	1	0
Auriculoventricular block	1	2
Coupling fixed	33	56
Coupling not fixed	15	26

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DIGITALIS BIGEMINY*

An Analysis of Fifty Cases

ELLIOT L SAGALL, M D,† AND LOUIS WOLFF, M D‡

BOSTON

BIGEMINAL rhythm following the administration of digitalis is frequently encountered and is generally accepted as a sign of digitalis intoxication. The characteristics of this type of coupled rhythm, however, are not clearly defined, and there is little in the literature concerning the subject. The present investigation was undertaken in an attempt to elucidate the features of digitalis bigeminy that might be of practical clinical value.

METHODS

The patients studied were limited to those in whom paroxysmal or constant ventricular bigeminy was demonstrated electrocardiographically. Of the electrocardiograms taken from 1929 to 1948 at the Beth Israel Hospital, Boston, 183 separate cases of bigeminy in 174 patients were satisfactory for the purposes of this study. The classification of electrocardiographic bigeminal rhythms presented by Parsonnet et al¹ was employed.

The clinical records, progress notes and medication charts were examined in each case to evaluate the role of digitalis in the production of the arrhythmia. In 82 cases, referred to below as the nondigitalis or control group, digitalis had not been administered prior to the appearance of bigeminy. In 101

cases digitalis bodies had been administered during the month preceding the appearance of bigeminal rhythm. Digitalis was considered to be a definite causal factor in 50 of these because bigeminy appeared for the first time shortly after a large initial dose, after increase in the maintenance dose, or after a profuse diuresis without change in the maintenance dose. In these cases, referred to below as the digitalis group, confirmatory evidence of this relation was afforded by the disappearance of the arrhythmia with omission or reduction in the dosage of the drug, or by the presence of other symptoms or signs of digitalis intoxication. In a few cases, after reversion to normal rhythm, bigeminy was again induced by an increased dose of digitalis. The relation between digitalis and bigeminy in the remaining 51 cases could not be established or excluded, and these cases were classified as indeterminate.

RESULTS

In 172 cases bigeminy resulted from extrasystolic contractions occurring after each normal beat. The premature beats arose in the ventricles in 107 cases, in the auricles in 42, in the sinus node in 19, and in the auriculoventricular node in 4. In the remaining cases coupling was due to a shifting auriculoventricular block in 7, sinus pauses in 1, and fortuitous pairing of ventricular beats in auricular fibrillation in 3.

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Comparison of the Digitalis and Nondigitalis Groups

Type and dosage of digitalis At the time of appearance of bigeminy whole-leaf digitalis was being administered orally in 45 cases and digitoxin in 3. In 2 cases a mixture of digitalis glycosides (digalen) was given intramuscularly. The amount of digitalis given and the length of time during which the patient had received the medication before the appearance of bigeminy varied considerably. In most cases bigeminy appeared when the maintenance dose was increased, even in such small amounts as 0.05 to 0.1 gm. In 4 cases a profuse diuresis induced by parenteral administration of mercurial diuretics resulted in bigeminal rhythm without an increase in the maintenance dose of digitalis. In another case the same phenomenon was observed after a massive gastrointestinal hemorrhage.

Age and sex The average age of the patients in the digitalis group was 53.9 years, whereas in the

group, and auricular and sinus nodal extrasystolic bigeminy were almost as common (Table 4).

The features of the ventricular extrasystolic bigeminy in the two groups are shown in Table 5.

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HEART DISEASE	DIGITALIS GROUP NO. OF CASES	NONDIGITALIS GROUP NO. OF CASES
None	0	19
Rheumatic	21	4
Rheumatic and hypertensive	4	0
Rheumatic and coronary	1	0
Hypertensive	4	15
Hypertensive and coronary	10	17
Coronary	6	21
Syphilis	1	1
Calcareous aortic stenosis	1	1
Congenital	1	1
Indeterminate	1	5
Totals	50	82

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AGE	DIGITALIS GROUP	NONDIGITALIS GROUP
0-10	0	3
11-20	0	0
21-30	6	2
31-40	2	7
41-50	10	5
51-60	15	21
61-70	12	27
71-80	4	13
81-90	1	1
Male	22	46
Female	28	36

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TABLE 3 Basic Cardiac Rhythms of Patients with Digitalis and Nondigitalis Bigeminy

RHYTHM	DIGITALIS GROUP NO. OF CASES	NONDIGITALIS GROUP NO. OF CASES
Normal sinus	28	31
Auricular fibrillation	21	0
Auricular flutter	1	0
Auriculoventricular nodal	0	1
Totals	50	82

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disease, but more often complicated rheumatic heart disease and auricular fibrillation. Although there was marked individual variation in the amount of drug administered prior to the development of the arrhythmia, bigeminy in the majority of cases was a sensitive manifestation of toxicity, appearing for the first time after a small increase in the maintenance dose.

The electrocardiographic features of digitalis bigeminy, as a rule, differed from those in the group that was unrelated to digitalis. Digitalis bigeminy was almost always due to ventricular extrasystoles, and the ventricular premature beats were more likely to be multifocal in origin and to arise in the right ventricle, in no case did they originate from the basal portion of the ventricles. Rare cases of coupled rhythm arising from other causes were also recorded in the digitalis group. One case of coupling due to shifting auriculoventricular block was similar to that described by Lutembacher.⁷ In addition 1 case each of bigeminy due to sinoauricular block and to auricular and auriculoventricular nodal premature beats were encountered.

In many of our cases bigeminal rhythm was the only evidence of digitalis intoxication. The appearance of an arrhythmia as the first sign of digitalis poisoning has also been noted by Marvin,⁸ who reported 5 cases of ventricular tachycardia following excessive dosage of digitalis. Similarly, Grishman and Dack,⁹ in a recent study of 50 cases of digitalis toxicity, observed that various arrhythmias were often the only clinical manifestation of overdosage. There was no definite relation between the appearance of digitalis bigeminy and other manifestations of toxicity. The arrhythmia preceded, followed or developed simultaneously with the other signs and symptoms.

The seriousness of digitalis bigeminy is difficult to evaluate. White¹⁰ has stated that the appearance of bigeminal rhythm "indicates that a considerable percentage of a lethal dose has been given, probably close to 75 per cent." The possibility that further administration of digitalis to a patient who has developed coupling will lead to serious or fatal poisoning is apparent. Bigeminy, therefore, is a danger signal that cannot be ignored. In some or all of the 14 fatal cases in our series death may have been due to digitalis, since all patients had received large amounts of the drug.

The conditions that must be present in the myocardium for the production of bigeminy are unknown. Although bigeminy occurs in the absence of heart disease, clinical observations indicate that digitalis bigeminy occurs only in the presence of a diseased myocardium. This thesis is further substantiated by animal experiments and observations on the effect of large doses of digitalis in people with normal hearts. In the intact mammalian heart in situ irregular extrasystoles occur only in the last stages of digitalis poisoning, and bigeminy is never

produced.¹¹ The subendocardial hemorrhages and necroses induced in animal hearts by large amounts of digitalis,¹²⁻¹³ therefore, apparently do not increase the susceptibility to bigeminy. In human subjects with normal hearts who have ingested large amounts of digitalis bodies in suicidal attempts, repeated electrocardiograms have revealed a variety of serious arrhythmias and only rare extrasystoles, but no bigeminy.⁵⁻¹⁴⁻¹⁶ Digitalis was administered to 100 persons without heart disease by Wolff,¹⁷ and although repeated electrocardiograms revealed definite changes in the ST segments, T waves and PR intervals, only two ventricular premature beats were noted in 300 electrocardiograms. In the recent New York insurance fraud large doses of digitalis were ingested by a number of persons in an attempt to simulate heart disease, and in this group only occasional ventricular extrasystoles were detected and bigeminy was not reported.¹⁸

SUMMARY AND CONCLUSIONS

One hundred and eighty-three cases of bigeminy were studied in regard to the etiologic relation between digitalis and the coupled rhythm. Bigeminy was associated with digitalis in 50 cases and unrelated to digitalis in 82. In 51 the relation was indeterminate.

Bigeminal rhythm is common in patients with or without organic heart disease who have not received digitalis, and in 39 per cent is ventricular extrasystolic in mechanism.

Bigeminal rhythm may be induced in patients with organic heart disease by digitalis and is almost always due to ventricular extrasystoles.

The ventricular extrasystolic bigeminy associated with digitalis differs from that unrelated to digitalis in that the ventricular premature beats are more commonly multifocal and arise in the right ventricle. In nondigitalis bigeminy ectopic contractions arise more frequently in the left or basal portions of the ventricles.

Digitalis bigeminy occurs in all types of heart disease and with a variety of basic rhythms, but more often complicates rheumatic heart disease and auricular fibrillation.

Bigeminy may be induced by purified digitalis derivatives as well as the whole-leaf product.

Digitalis bigeminy is a sensitive manifestation of toxicity and may appear with a small increase in the maintenance dose.

Bigeminy may be the only evidence of digitalis intoxication and may precede, follow or develop simultaneously with other manifestations of toxicity.

Bigeminy may be a serious sign of digitalis toxicity and in some cases may herald sudden death.

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Other manifestations of digitalis toxicity The relation between the appearance of bigeminy and other signs and symptoms of digitalis intoxication was inconsistent. In some cases bigeminy was the first or only manifestation of digitalis overdosage, in others it developed concomitantly with or followed the appearance of anorexia, nausea, vomiting or visual disturbances. In 7 cases digitalis overdosage produced paroxysmal arrhythmias in addition to bigeminy. The abnormal rhythms were ventricular tachycardia in 4 (2 with bidirectional complexes), auricular flutter in 1, auricular fibrillation in 1, and both paroxysmal auricular fibrillation and auriculo-ventricular nodal tachycardia in 1. In 6 of these cases bigeminy was recorded after cessation of the

Edens and Huber³ recorded 29 cases of digitalis bigeminy, but in only 6 were electrocardiograms taken. In 27 the bigeminal rhythm was due to ventricular extrasystoles as determined by jugular-pulse tracings, and in the remaining 2 the mechanism was indeterminate. Congestive heart failure was present in all, and 13 patients had auricular fibrillation. These authors concluded that digitalis bigeminy occurred only in hypertrophied hearts that manifested decreased muscular efficiency. Because 23 patients died within two years of the appearance of bigeminy digitalis coupling was considered to indicate a poor prognosis.

Gold and Otto⁴ reported the cases of 45 patients with digitalis bigeminy. All had organic heart disease, the etiologic type being arteriosclerotic in 8, rheumatic in 16, syphilitic in 4, not specified in 2 and unknown in 15. The basic cardiac rhythm was auricular fibrillation in 35 and normal sinus rhythm in 10. In the latter group 8 patients later developed auricular fibrillation. In all cases bigeminy was due to ventricular premature beats. In contrast to Edens and Huber,³ the authors believed that susceptibility to digitalis bigeminy did not indicate a grave prognosis beyond that due to the underlying heart disease and the functional capacity of the heart.

In 1926, Gallavardin⁵ presented a clinical discussion of digitalis coupling and summarized the previous French literature. He stated that although others had emphasized the frequency of digitalis bigeminy in patients with enlarged hearts with mitral disease, the arrhythmia could occur in patients with all types of heart disease and with normal sinus rhythm as well as auricular fibrillation. The bigeminy that he encountered was always due to ventricular extrasystoles, which in the majority of cases were polymorphic. He believed that digitalis bigeminy occurred only in the presence of a diseased myocardium, for in his experience the arrhythmia was never induced by digitalis in normal hearts.

Scherf and his co-workers have reported a number of experimental and clinical observations regarding digitalis extrasystoles and bigeminy. Their findings and conclusions have recently been summarized by Scherf and Boyd.⁶ They favor the view that digitalis alone will not produce extrasystoles or bigeminy and that other unknown conditions, which vary considerably from case to case, must be present for the induction of bigeminy by the drug. In their experience the arrhythmia was precipitated by digitalis more easily in patients with severe heart disease, and the extrasystoles in most cases arose from multiple foci.

On the whole, the results of our study are in agreement with the findings discussed above. In our cases bigeminal rhythm was induced by purified digitalis derivatives as well as the whole-leaf product. There was no specific relation to age or sex. It appeared in patients with all types of heart

TABLE 5 *Electrocardiographic Features in 46 Cases of Digitalis and 32 of Nondigitalis Ventricular Extrasystolic Bigeminy*

ELECTROCARDIOGRAPHIC FEATURE	DIGITALIS GROUP	NONDIGITALIS GROUP
Focality		
Unifocal	32	31
Multifocal	14	1
Point of origin*		
Right ventricle	21	7
Left ventricle	9	12
Both right and left ventricles	8	0
Apical portion	3	0
Basal portion	0	10
Septal portion	2	0
Indeterminate origin	3	3
Coupling		
Fixed	34	24
Not fixed	12	8

* Determined by the method described by Burch and Winsor.⁷

paroxysmal arrhythmia, in 1 it appeared first, and was followed by paroxysmal tachycardia consequent to the administration of additional amounts of digitalis.

Duration of digitalis bigeminy Although in most cases bigeminy was a temporary phenomenon, in a few cases the bigeminal rhythm, once induced by digitalis, persisted for many days after omission of the drug and in some was apparently permanent. Fourteen patients in the digitalis group died during the period of observation. In 11 cases additional amounts of digitalis had been given despite the presence of bigeminal rhythm, and in 3 bigeminy appeared for the first time on the day of death.

DISCUSSION

Despite its clinical importance and the frequency with which it is encountered digitalis bigeminy has attracted but little attention, especially in the American literature. Most publications concerning digitalis bigeminy antedate 1930, and since then only an occasional reference to the subject has been made. As far as could be determined the only clinical analyses of relatively large series of cases were those of Edens and Huber³ in 1916 and Gold and Otto⁴ in 1926.

ment and not to adhere too strictly to a rigid schedule. Eleven cases were treated over one hundred days. The longest treatment period was one hundred and seventy-five days. Forty patients received streptomycin for forty-two days or less, and in 41 cases the length of treatment varied between fifty and one hundred days. A daily dosage of 0.5 gm divided into two intramuscular injections was used in 37 cases. A dose of 1.0 gm daily was received by 55 patients. In children only half the dose was used — 0.5 and 0.25 gm respectively.

SENSITIVITY

In the more recently treated cases, a dosage of 1.0 gm a day for forty-two days was adopted. Such a treatment schedule conforms with the present views of streptomycin fastness,¹ which is assumed to develop between thirty and sixty days in the majority of cases. In this study no attempt was made to demonstrate fastness by laboratory methods, but clinical observation in some cases of tuberculosis of the kidney bore out the fact that after as early as thirty days any improvement stops and decrease of urinary urgency and frequency ceases. Further administration of streptomycin in such cases was followed by aggravation of clinical symptoms.

SECOND COURSE

Streptomycin fastness is probably the reason why a second course² with streptomycin usually gives disappointing results. Six patients received a second course of streptomycin. None of these cases gave excellent results. In 3 cases good results were obtained, and 3 cases had to be labeled as failures. It is therefore advisable to determine the sensitivity to streptomycin before a second course is undertaken.

RESULTS

In this study 157 lesions were treated. Excellent results were obtained in 50 per cent, and good results in 36 per cent, 14 per cent were failures.

A summary of the results is presented in Table 1.

Recurrence

Recurrence or development of a new lesion during or after a course of streptomycin was seen in 7 cases, or 8 per cent. The impression was gained that the reactivated or newly developed lesion was altered and of less intensity. Two spinal lesions, for instance, diagnosed shortly after the beginning of streptomycin therapy, showed minimal evidence of destruction and soon became inactive.

Sinuses

Best results were achieved in the treatment of sinuses. A total of 48 tuberculous sinuses in 33 patients were treated, 67 per cent were closed in an average of sixty-two days, 33 per cent improved, and in none had failure to be conceded. The sinuses

had drained for an average of nine hundred and fifty-four days before treatment with streptomycin was started. These favorable results cannot be credited entirely to streptomycin since penicillin was frequently given before or simultaneously with streptomycin to combat secondary infection. In addition, a dressing technic comparable to the sterile requirements of surgical wounds was applied to prevent introduction of new pyogenic organisms into the sinuses.

Bones and Joints

Fifty-seven lesions of bones and joints were treated with streptomycin. Excellent results were obtained in 35 per cent, and good results in 47 per cent, and 18 per cent failed to respond to the drug. The evaluation of bone lesions is extremely difficult —

TABLE 1 Results of Streptomycin Therapy in 157 Tuberculous Lesions

LESION	NO OF CASES	EXCELLENT RESULT	GOOD RESULT	FAILURE
		NO OF CASES	NO OF CASES	NO OF CASES
Sinuses	48	32 (67%)	16 (33%)	—
Genitourinary infection	23	12 (52%)	3 (13%)	8 (35%)
Bones and joints	57	20 (35%)	27 (47%)	10 (18%)
Skin, mouth and pharynx	3	3	—	—
Lymph nodes	5	2	3	—
Pentostitis	3	1	2	—
Tendosynovitis and bursitis	4	2	—	—
Mastoid	4	1	5	—
Paraplegia	4	2	1	1
Meningitis	2	—	—	2
Pulmonary	2	2	—	—
Totals	157	77 (50%)	57 (36%)	23 (14%)

bone changes are slow, and x-ray signs of healing are not immediately apparent. Gain in clarity and distinctness in the x-ray appearance, and repair and arrest of the destructive process could be observed either immediately after termination of treatment or within the next few months. Changes in the soft tissues surrounding the lesion are seen more promptly, as manifested in decrease or disappearance of abscess shadows and joint effusions. As valuable as this acceleration in the healing process may be, the emphasis should be placed upon the fact that streptomycin renders the tuberculous patient operable in a much shorter time than conventional treatment does and that it permits the surgeon to enter diseased tissue with less risk of propagation of the tuberculous process, thus allowing greater freedom in the choice of operation and more radical procedures. Under the protection of streptomycin, radical extirpation of a tuberculous bursa and removal of a sequestered femoral head were carried out and were followed by an uneventful postoperative course not marred by sinus formation or wound breakdown.

Genitourinary Tract

Twenty-three cases of tuberculous kidney were treated. Fifty-two per cent gave excellent results,

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STREPTOMYCIN IN THE TREATMENT OF EXTRAPULMONARY TUBERCULOSIS*

Early Results

KURT JELLINEK, M D †

MIDDLEBORO, MASSACHUSETTS

THIS report deals with 92 cases of extrapulmonary tuberculosis treated with streptomycin in various amounts and over different lengths of time. In all cases the lesions were proved to be tuberculous by guinea-pig inoculation or x-ray study or both. No pulmonary activity was found except in 2 cases, in which an incipient pulmonary lesion was readily controlled by streptomycin. In the majority of these cases residua from previous pulmonary infection with tuberculosis could be demonstrated. In every case the intradermal tuberculin reaction was positive. Many of these patients had more than one tuberculous lesion, and 157 active lesions were present. No consideration was given to lesions arrested prior to streptomycin treatment. A tuberculous infection of one or both kidneys with urinary-bladder involvement was regarded as a single entity. A bone sinus originating from a tuberculous arthritis was counted as two separate lesions because of the somewhat different course these lesions might take, the bone sinus might heal promptly, but the tuberculous process in the joint might continue to smolder.

CLASSIFICATION

To obtain a clear-cut picture, the results were graded into excellent, good and failure. The term "excellent" was used in cases that fulfilled the following conditions: no material positive for tuberculosis on guinea-pig inoculation was obtainable, marked improvement in the general condition, cessation of pain, closure of sinuses, disappearance of palpable abscesses and freedom from symptoms were achieved, and subsidence of activity by x-ray

checks, disappearance of abscess shadows and effusions in and at the bones and joints were observed.

"Good" results were claimed when improvement in the general condition was noted, with a decrease of symptoms, such as diminished discharge from sinuses, reduction in the size of lymph-nodes and abscesses, improvement in the x-ray appearance of lesions and partial return of function in paralysis.

The term "failure" is self-explanatory.

By necessity this classification has to be arbitrary. An absolute and clear distinction between the effects of streptomycin and the results of sanatorium care combined with surgical operation could not be undertaken. It might be well to point out now, and again later, that the reported results could only be obtained under sanatorium care. As only one to nine months have elapsed since termination of streptomycin treatment, this report must be regarded as preliminary.

DOSAGE

One of the main difficulties of streptomycin therapy was, and still is, the selection of the proper dosage.^{1, 2} The initial recommendation to give streptomycin for prolonged periods (one hundred and twenty days and more) in high dosage (30 gm and more per day) divided into multiple intramuscular injections was soon abandoned because of the high incidence of untoward reactions. Only 3 cases in this study were treated according to the schedule mentioned above, and even in these cases the daily dose had to be dropped quickly from 30 to 20 gm or less, because of severe dizziness and beginning deafness.

Owing to the existing uncertainty concerning dosage an effort was made to individualize the treat-

* From the Lakeville State Sanatorium

† Senior physician, Lakeville State Sanatorium

ECONOMIC ASPECTS

Any treatment that is capable of shortening the exceedingly long course of tuberculosis will have profound effects on the economic, social and psychologic aspects of the disease. In the series of cases cited, the average time from onset of the disease to the beginning of streptomycin treatment was three years, eight months and six days. To salvage patients after such long suffering and to return them to active life after an average treatment period of one year is a significant achievement. The saving in taxpayer's money and the elimination of sources of infection are important considerations.

A most gratifying result is the change in the patients' psychology. The feeling of resigned suffering and doom and the passive acceptance has given way to hope and confidence. The doctor on a tuberculous ward is no longer a dispenser of analgesics and hypnotics, but is able to prescribe and direct active treatment.

CONCLUSION

It can be concluded that streptomycin is a valuable asset in the treatment of extrapulmonary tuberculosis. The first course is usually more effective

than a second course, and proper timing of the first course is therefore important. In surgical cases its use just prior to or shortly after surgery is recommended. A daily dose of 1.0 gm in adults for forty-two days is used at present. Encouraging results were obtained in tuberculosis of the bones and joints with and without draining sinuses, of the genitourinary tract, in paraplegia due to Pott's disease and in lesions of the skin and pharynx. Mild side reactions, if encountered, do not preclude continuation of treatment. More severe reactions, which interfere with the general condition of the patient, should be regarded as indications to terminate streptomycin treatment. Second courses have little, if any, value unless definite sensitivity of the bacilli to streptomycin can be demonstrated. Best results are achieved under a sanatorium type of treatment combined with surgical operation when indicated.

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PRACTICAL CONSIDERATIONS OF CLINICAL OXYGEN LACK*

CHARLES S. HOUSTON, M.D.

EXETER, NEW HAMPSHIRE

WHEN confronted with a patient whose problem may in part be due to oxygen lack, the physician often bases his opinion upon the presence or absence of dyspnea and cyanosis, forgetting that these important signs are but two of the many changes due to anoxia. He may not realize that either or both may be present even though oxygenation is adequate, and he may not appreciate that both may be absent even when oxygen lack is severe. In its classic form anoxia may be recognized at a glance, but in other circumstances, not infrequently encountered in practice, the most elaborate laboratory procedures cannot give a definitive evaluation of the adequacy of the oxygen supply to the body. The best that a practitioner can hope to do in this complex situation is to maintain a high index of suspicion for the presence of anoxia in certain pathologic conditions, and to institute therapeutic or prophylactic procedures when certain signs and symptoms of anoxia are first noted. Some of the common conditions that frequently result in anoxia, as well as the more reliable indications of anoxia, are discussed in this paper.

CAUSES OF OXYGEN LACK

It is the relation of oxygen supply to demand, rather than either alone, that determines whether or not tissue anoxia is present. If tissue demand exceeds supply, no matter how great the latter may be, anoxia develops at once, for oxygen cannot be stored. Therefore, conditions that increase the bodily need for oxygen (exertion, fever and hyperthyroidism, for example) cause anoxia unless supply is accordingly increased, just as interference with oxygen supply (high altitude, pulmonary and circulatory disease and so forth) does unless tissue demand is decreased. Very often a disease both decreases supply and increases demand (pneumonia with fever, cardiac failure and exertion), which doubly impairs tissue oxygenation. Most physicians are aware of the seriousness of febrile disease, especially pulmonary disease, in the patient with hyperthyroidism. Discrepancy between supply and demand is further illustrated by the difficulty experienced on exertion by anemic persons, by those with chronic pulmonary disease and by patients with circulatory insufficiency. The high mortality that attends pneumonia in visitors

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From the Exeter Clinic.

and 13 per cent good results, and 35 per cent were failures. The result of treatment of tuberculosis of the kidney and bladder had previously been extremely disappointing, and even after removal of the diseased kidney the majority of patients continued to excrete urine containing tubercle bacilli. Patients with bilateral involvement appeared doomed, and early detection during the period of unilateral involvement followed by radical surgery was therefore the only hope. The introduction of streptomycin promises a radical change for the better.

Out of the 15 cases in which nephrectomy was performed and in which the urine remained positive for tuberculosis after operation, 74 per cent were rendered negative, and no reversal of urine took place in only 13 per cent. In the nonoperative group treated with streptomycin the rate of failures ran as high as 75 per cent.

Early diagnosis and radical operation are still imperative, but by the administration of streptomycin shortly before and after nephrectomy the percentage of clinical arrest of the disease is greatly improved. At the same time, the development of postoperative kidney sinuses is in many cases eliminated or early closure of the existing sinuses ensured.

In a comparative study, not yet completed, dealing with postoperative results in tuberculous kidneys before the streptomycin era, urine free of tubercle bacilli was obtained in only 38 per cent of cases.

Fear that a patient with impaired kidney function will tolerate streptomycin poorly is not unfounded, and the incidence of side reactions is slightly higher (38 per cent) than that in cases with unimpaired kidney function. But by the employment of dosages not exceeding 10 gm daily, these side reactions rarely reach serious proportions. A slight rise in the nonprotein nitrogen during the treatment was seen. The greatest increase was 14 mg per 100 cc.

Lupus Vulgaris

The limited experience gained from 2 cases of lupus vulgaris, 1 involving the face and neck and the other involving the mucous membranes of the nose, confirmed other reports,³ that streptomycin causes prompt arrest. The same excellent results were obtained in a pharyngeal lesion.

Tuberculous Lymph Nodes

Of 5 cases of tuberculous adenitis, 2 reacted excellently and 3 showed improvement characterized by diminution of the size of the lymph nodes and closure of existing sinuses. Hard indurated nodes showed slow response.

Tuberculous Peritonitis

Three cases of tuberculous peritonitis were treated, 1 with excellent results, and 2 with marked im-

provement. Abatement of fever, cessation of pain and drying up of ascites were observed. These results were confirmed by x-ray films, which revealed increase in clarity and decreasing density of the abdominal structures. The more acute the disease, the more dramatic the rate of improvement.

Tuberculous Mastoiditis

Satisfactory results were also obtained in 4 cases of mastoiditis. One of these patients responded excellently. Not only was improvement noted in the x-ray appearance of the mastoid bones but also the hearing became more acute, the discharge from the chronically infected ears stopped or diminished, and the patients became free of pain.

Tuberculous Bursitis and Tendosynovitis

Four cases of tuberculous bursitis and tendosynovitis were treated — 2 with excellent results and 2 with good results as evidenced in a decrease of swelling and painless motion.

Paraplegia

Series of 3 or 4 cases have only limited significance and do not show more than a trend. Nevertheless, the results in even a small series of paraplegic cases were regarded as important. Paraplegia during the course of Pott's disease is not an uncommon occurrence. This paraplegia is rarely the result of the spinal deformity, but is caused either by pus formation or by tuberculous granulation tissue pressing against the cord.

Of the 4 patients treated with streptomycin, 2 responded with complete restitution of muscular power and return of normal reflex activity. One patient improved considerably. The fourth, a paraplegic patient of long standing who had not been helped by extensive surgical procedures, did not respond. At present 1 patient is under treatment, and the progress is quite promising.

SIDE EFFECTS

Owing to moderation in dosage, side effects were comparatively mild. Twenty-five per cent of the total cases showed some untoward effects. Vertigo was observed in 15 per cent, skin rash in 6 per cent, and vomiting, nausea and paresthesia of the lips or fingers in 2 per cent each. Only in 6 cases was it necessary to discontinue streptomycin. One of these cases was especially instructive, since the patient had become sensitized by the use of streptomycin ointment. A form of exfoliative dermatitis developed three days after intramuscular use of streptomycin. This dermatitis healed promptly after discontinuation of the drug. None of the side effects observed were permanent, although in some cases, which had received higher dosage, vertigo persisted for months.

alkalosis resulting from hyperventilation causes peripheral vasoconstriction and thereby may cause significant tissue anoxia

From these brief paragraphs it is apparent that cyanosis is often present even though oxygenation is adequate, and that severe anoxia may be present without clinically detectable cyanosis. Furthermore, oxygen lack is only one of the many causes of dyspnea, and sometimes an ineffective one at that.

The mental signs of anoxia may be subtle and easily mistaken for primary neurologic disease. Mental confusion, emotional lability, errors in judgment, inability to concentrate, headache or gross tremors are frequently caused by oxygen lack alone and may be a principal evidence of its presence. These signs and symptoms are often seen in elderly persons with arteriosclerosis, in patients with chronic pulmonary disease, anemia, carbon monoxide poisoning, and other conditions that cause chronic, low-grade tissue anoxia.

Circulatory Effects

Among the circulatory changes that occur, tachycardia is regarded by some workers as one of the most reliable signs of oxygen lack, and an indication of the need for therapy. The increase in heart rate, as well as an increase in stroke output, is an adaptive mechanism by which the body attempts to deliver a greater minute volume of oxygen-carrying blood in an effort to decrease the oxygen lack. An immediate increase in the apparent red-cell count occurs within forty-eight hours of anoxia, owing to hemoconcentration, the true increase in total red cells requires a longer time (seven to fourteen days).

Two dramatic and important responses to anoxia were seen during the training exposure of young aviators to high-altitude anoxia in decompression chambers during the war. If the oxygen lack were produced rather slowly (twenty to forty minutes) and in moderate degree (18,000 feet, or 10 per cent oxygen), about 1 or 2 per cent of these men developed pallor, sweating, nausea, bradycardia, fall in blood pressure and collapse. This syndrome, commonly known as vasovagal syncope or primary shock, is a nonspecific response to a wide variety of stimuli, among which are hunger, fear, emotional stress and pain. When full oxygen was restored, the men recovered consciousness at once, though the other symptoms were prominent for an hour or longer. By contrast, if the oxygen lack were sudden (one or two minutes) and severe (30,000 feet, or 7 per cent oxygen) vasovagal syncope was rarely seen. Instead the men grew confused, the pulse rate was increased, blood pressure normal, or elevated, and muscular incoordination and sudden loss of consciousness occurred rapidly. All effects were immediately reversed with oxygen. There is good reason to believe that either of these clinical pictures can occur as a result of disease or injury caus-

ing anoxia, and either type of reaction may be very confusing to the physician. Vasovagal collapse caused by anoxia probably is often mistaken for shock, hemorrhage, adrenal insufficiency, birth injury and so forth.

Once oxygen lack is suspected as contributing to a given symptom complex, the physician must attempt to correct the discrepancy between oxygen demand and supply. Increasing supply by providing an atmosphere high in oxygen (by mask, tent or nasal catheter) will greatly help many conditions, particularly those in which oxygen lack is from environmental or pulmonary causes. In other conditions it is the transportation of oxygen that must be improved — by digitalis if the myocardium is weak or by transfusion if circulating hemoglobin is low. Often, it is sufficient merely to decrease the tissue demand for oxygen, by strict rest or reduction of high fever, or by correction of an abnormally elevated metabolic rate. Obviously, optimum therapy will increase supply, improve transportation and reduce demand by all appropriate measures.

The physician must be careful not to interfere with natural mechanisms that the body develops to decrease anoxia, of which increased respiration may be very important. If respiration is depressed (by morphine, strapping the chest, ill advised recumbency) mild anoxia may become severe, and alarming symptoms may result. I was recently responsible for such an event in an obese, elderly man who had experienced a very severe gastric hemorrhage. Owing to his anemia he showed some air hunger, which greatly increased when his temperature rose to 103°F during a transfusion reaction. Morphine, given to allay restlessness, depressed his respirations, and he became irrational and violent. When the morphine was discontinued and respirations again increased, the symptoms of cerebral anoxia improved, but not until his anemia was further corrected did all symptoms of anoxia disappear. It is worthy of note that at no time was he cyanotic, for his circulating hemoglobin (less than 5 gm) was fully oxygenated, even though he was severely anoxic. In this case obesity, fever and activity all increased the need for oxygen, whereas anemia and morphine-suppressed respiration decreased the supply.

If the physician suspects that a patient's mental confusion, irritability, dyspnea or tachycardia may be due in part to anoxia, it is not sufficient simply to give oxygen therapy. Every effort must be made to visualize the dynamics of oxygen lack, and therapy should include all the measures that increase supply, improve transportation and decrease demand. To increase the supply, treatment should increase inspired oxygen, facilitate respiration, correct anemia and improve circulation, to decrease demand, it should reduce activity (mental and physical), lower fever and diminish abnormally elevated basal metabolic rate.

to high altitudes and in patients with chronic pulmonary or cardiac disease is well known

Table 1 presents some of the common conditions that often cause clinically important oxygen lack

DETECTION OF ANOXIA

As in so much of medicine, a high index of suspicion is the first prerequisite for the detection of anoxia except in its most flagrant form. It is the

TABLE 1 *Outline of Causes of Tissue Anoxia*

I Oxygen Demand Normal — Oxygen Supply Decreased	
(a)	<i>Environmental</i> — low partial pressure of oxygen in inspired air (high altitude asphyxia)
(b)	<i>Pulmonary</i> — impaired respiratory exchange (emphysema, asthma, poliomyelitis) — diminished alveolar surface (pneumonia, infiltration, atelectasis) — impeded alveolar — arterial diffusion (pulmonary edema, fibrosis)
(c)	<i>Circulatory</i> — inadequate cardiac output (myocardial weakness, valvular disease, pericarditis) — inadequate or abnormal vascular bed (arteriosclerosis, arterial spasm, arteriovenous fistula, Paget's disease), — inadequate oxygen carrying power (anemia, carbon monoxide poisoning, methemoglobinemia)
(d)	<i>Tissue</i> — inadequate capillary flow (spasm, frostbite) — impeded capillary — tissue diffusion (?) (scleroderma, edema) — defective oxidation — reduction enzyme systems (cyanide poisoning, vitamin deficiency (?))
II Oxygen Demand Increased — Oxygen Supply Normal	
(a)	Generalized — exercise, fever, hyperthyroidism
(b)	Localized — infection

old story of "seek and ye shall find, seek not and ye find nothing."

Cyanosis

Cyanosis is, of course, the most reliable indication of anoxia. This blueness of the lips, nail beds and mucosa depends upon the absolute amount of reduced hemoglobin in the capillary blood rather than upon the proportion of reduced to oxygenated hemoglobin. Years ago Lundsgaard and Van Slyke¹ showed that a minimum of 5 gm. of reduced hemoglobin per 100 cc. of blood must be present in capillary blood before cyanosis is apparent. Under ordinary circumstances arterial blood is 95 to 98 per cent saturated with oxygen, decreasing as it passes through the capillaries to 70 per cent saturation in mixed venous blood. Therefore, 25 to 28 per cent of the circulating hemoglobin, or 3.0 to 3.5 gm., is the maximum amount of reduced hemoglobin present at any point along the capillary, and this is less than the 5.0 gm. necessary to produce cyanosis. If, however, the saturation of either mixed venous or arterial blood decreases, so that the average amount of reduced hemoglobin in the capillary is 5 gm. or more, cyanosis will appear. The polycythemic patient who may have as much as 20 or 25 gm. of hemoglobin per 100 cc. of blood will show cyanosis even under the ordinary conditions outlined above, because more than 5.0 gm. of reduced hemoglobin is present. By contrast, in severe anemia when circulating hemoglobin may be as low

as 5.0 gm. cyanosis can never appear, because this would require total reduction of all hemoglobin, a manifest impossibility. In less severe anemia, cyanosis may appear only when the oxygen lack is already very marked.

Furthermore, as Comroe and Botelho² have demonstrated, cyanosis is dependent not only upon variable factors in the patient but also upon the ability of observers to recognize color changes, and serious degrees of anoxia frequently go undetected without laboratory aid. Kubicek,³ referring to anoxia in poliomyelitis, makes the following observation:

Clinically, cyanosis has too frequently been regarded as the first sign of oxygen deficiency and as an indication that remedial therapy should only then be initiated. Unfortunately cyanosis is seldom detectable if the saturation of hemoglobin is above 80%. When cyanosis is first visible, the flow of oxygen from capillary blood to nerve may be reduced by at least 65%. This makes it obvious why patients with bulbar poliomyelitis who become cyanotic so frequently succumb.

When a well equipped laboratory is available, arterial blood is easily analyzed for oxygen content and capacity, but even these figures represent only the oxygen available at the arterial end of the capillary, arterial oxygen content gives no hint of the amount of oxygen delivered to the tissues, which can only be estimated approximately if mixed venous blood is simultaneously analyzed. No methods at present available indicate whether or not oxygen supply is equal to oxygen demand.

Dyspnea

Dyspnea, the second major symptom of oxygen lack, has been defined as the consciousness of the necessity for increased breathing. Oxygen lack does stimulate respiration, probably through the carotid body rather than by direct action on the respiratory center, but its effect is variable and often weak. An impressive and practical demonstration of the weak stimulus given by anoxia to respiration was seen in the course of the altitude-training program during the war, when thousands of healthy young aviators briefly lost consciousness from oxygen lack alone, often without significant increase in respiration.⁴ Patients of low sensitivity may overbreathe considerably and yet be unaware of dyspnea. Conversely, the hypersensitive person may feel unable to get his breath, even though his respiratory exchange is normal or slightly increased. Furthermore, since the purpose of respiration is not only to provide oxygen for the body but also to eliminate carbon dioxide, a disturbance of this elimination will also cause dyspnea, the hyperventilation of acidosis is due not to oxygen lack but to carbon dioxide excess. Finally, the hysterical or neurasthenic patient, or one with a cerebral lesion, may overbreathe to a severe degree even though no metabolic abnormality may be present initially. Carrier⁵ has recently indicated that the

alkalosis resulting from hyperventilation causes peripheral vasoconstriction and thereby may cause significant tissue anoxia

From these brief paragraphs it is apparent that cyanosis is often present even though oxygenation is adequate, and that severe anoxia may be present without clinically detectable cyanosis. Furthermore, oxygen lack is only one of the many causes of dyspnea, and sometimes an ineffective one at that.

The mental signs of anoxia may be subtle and easily mistaken for primary neurologic disease. Mental confusion, emotional lability, errors in judgment, inability to concentrate, headache or gross tremors are frequently caused by oxygen lack alone and may be a principal evidence of its presence. These signs and symptoms are often seen in elderly persons with arteriosclerosis, in patients with chronic pulmonary disease, anemia, carbon monoxide poisoning, and other conditions that cause chronic, low-grade tissue anoxia.

Circulatory Effects

Among the circulatory changes that occur, tachycardia is regarded by some workers as one of the most reliable signs of oxygen lack, and an indication of the need for therapy. The increase in heart rate, as well as an increase in stroke output, is an adaptive mechanism by which the body attempts to deliver a greater minute volume of oxygen-carrying blood in an effort to decrease the oxygen lack. An immediate increase in the apparent red-cell count occurs within forty-eight hours of anoxia, owing to hemoconcentration, the true increase in total red cells requires a longer time (seven to fourteen days).

Two dramatic and important responses to anoxia were seen during the training exposure of young aviators to high-altitude anoxia in decompression chambers during the war. If the oxygen lack were produced rather slowly (twenty to forty minutes) and in moderate degree (18,000 feet, or 10 per cent oxygen), about 1 or 2 per cent of these men developed pallor, sweating, nausea, bradycardia, fall in blood pressure and collapse. This syndrome, commonly known as vasovagal syncope or primary shock, is a nonspecific response to a wide variety of stimuli, among which are hunger, fear, emotional stress and pain. When full oxygen was restored, the men recovered consciousness at once, though the other symptoms were prominent for an hour or longer. By contrast, if the oxygen lack were sudden (one or two minutes) and severe (30,000 feet, or 7 per cent oxygen) vasovagal syncope was rarely seen. Instead the men grew confused, the pulse rate was increased, blood pressure normal, or elevated, and muscular inco-ordination and sudden loss of consciousness occurred rapidly. All effects were immediately reversed with oxygen. There is good reason to believe that either of these clinical pictures can occur as a result of disease or injury caus-

ing anoxia, and either type of reaction may be very confusing to the physician. Vasovagal collapse caused by anoxia probably is often mistaken for shock, hemorrhage, adrenal insufficiency, birth injury and so forth.

Once oxygen lack is suspected as contributing to a given symptom complex, the physician must attempt to correct the discrepancy between oxygen demand and supply. Increasing supply by providing an atmosphere high in oxygen (by mask, tent or nasal catheter) will greatly help many conditions, particularly those in which oxygen lack is from environmental or pulmonary causes. In other conditions it is the transportation of oxygen that must be improved — by digitalis if the myocardium is weak or by transfusion if circulating hemoglobin is low. Often, it is sufficient merely to decrease the tissue demand for oxygen, by strict rest or reduction of high fever, or by correction of an abnormally elevated metabolic rate. Obviously, optimum therapy will increase supply, improve transportation and reduce demand by all appropriate measures.

The physician must be careful not to interfere with natural mechanisms that the body develops to decrease anoxia, of which increased respiration may be very important. If respiration is depressed (by morphine, strapping the chest, ill advised recumbency) mild anoxia may become severe, and alarming symptoms may result. I was recently responsible for such an event in an obese, elderly man who had experienced a very severe gastric hemorrhage. Owing to his anemia he showed some air hunger, which greatly increased when his temperature rose to 103°F during a transfusion reaction. Morphine, given to allay restlessness, depressed his respirations, and he became irrational and violent. When the morphine was discontinued and respirations again increased, the symptoms of cerebral anoxia improved, but not until his anemia was further corrected did all symptoms of anoxia disappear. It is worthy of note that at no time was he cyanotic, for his circulating hemoglobin (less than 5 gm) was fully oxygenated, even though he was severely anoxic. In this case obesity, fever and activity all increased the need for oxygen, whereas anemia and morphine-suppressed respiration decreased the supply.

If the physician suspects that a patient's mental confusion, irritability, dyspnea or tachycardia may be due in part to anoxia, it is not sufficient simply to give oxygen therapy. Every effort must be made to visualize the dynamics of oxygen lack, and therapy should include all the measures that increase supply, improve transportation and decrease demand. To increase the supply, treatment should increase inspired oxygen, facilitate respiration, correct anemia and improve circulation, to decrease demand, it should reduce activity (mental and physical), lower fever and diminish abnormally elevated basal metabolic rate.

SUMMARY

The common causes of clinically important oxygen lack are presented, together with the more prominent signs and symptoms that help in diagnosis. Cyanosis and dyspnea, though most reliable, may be absent in severe anoxia, and present even when oxygenation is adequate. Mental confusion and tachycardia are helpful and suggestive signs. The physician must realize that discrepancy between oxygen supply and demand is the cause of anoxia, and therapy

should include not only methods of increasing supply, but also measures that improve transportation and decrease tissue demand.

75 Front Street

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MEDICAL PROGRESS

ORAL SURGERY

KURT H. THOMA, D. M. D., F. D. S. R. C. S. (ENG.)*

BROOKLINE, MASSACHUSETTS

A NEW era of oral surgery has begun. In 1945 the American Society of Oral Surgeons appointed a seven-member committee and authorized them to form a certifying board and to conduct examinations for the certification of specialists in oral surgery. The American Board of Oral Surgery was incorporated under the laws of the State of Illinois in 1946 and subsequently approved by the Council on Dental Education of the American Dental Association. The Board conducted its first examinations in February, 1947. Among the qualifications¹ required of the applicant are the following:

Graduation from a recognized dental school in the United States or Canada.

Practice devoted exclusively to oral surgery for five years or more, including graduate training.

Graduate study in oral surgery for a period of two years or more in a recognized graduate school or hospital, or under the auspices satisfactory to the Board. (This period of training shall cover the clinical and technical phases of oral surgery, and the basic sciences as they are related to oral surgery.)

It is the aim of the Board that societies representing the specialty of oral surgery, teaching institutions, hospitals and Government services shall require the certificate of the Board for admission to the special societies and for advancement in hospitals, teaching institutions and Government services.

HISTORY

It may be interesting to look over the shoulder of time and review how this specialty was de-

veloped. At the time of Morton (the dentist who first demonstrated publicly the use of ether for the relief of pain in dentistry and surgery), no surgical specialties had evolved. By reason of their particular skill and interest in treating certain diseases, some practitioners attracted patients who had heard of their special ability and soon were obliged to limit their practices to narrower fields. A striking example is Simon P. Hullihen, who made a wide reputation with operations for harelip, cleft palate and cancer of the jaws. A pioneer in this field and a foremost man of his time, he was given an honorary D. D. S. and an honorary M. D. degree.

James E. Garretson,² influenced by the brilliant achievements of Hullihen, published the first comprehensive American text on oral surgery in 1869. He recognized that there was an isolated field in surgery that had been neglected, being somewhere between medicine and dentistry. He pointed out in the preface of the second edition of his book published in 1873 that there is a great need for special training in this field, which, if taken in hand by medicine, suffers from want of special information and knowledge, and if taken care of by dentistry meets with disaster because of lack of surgical training and operative skill. A reviewer of Garretson's text stated: "This book fills a hitherto unoccupied place in the literature, and bridges the chasm which has separated dentistry from medicine."

The first recognition of the specialty of oral surgery came in 1869 when James E. Garretson was appointed to the Hospital of the University of Pennsylvania with the title of "oral surgeon."

Though the specialty did not receive a very cordial reception at first, Garretson and his contemporaries, who limited their practices to surgery of the mouth and jaws, continued to develop this specialty. These men had strong personalities, became great teachers

*Emeritus professor of oral surgery and Charles A. Brackett Professor of Oral Pathology, Harvard University; lecturer in oral surgery, Graduate School of Medicine, University of Pennsylvania; member, Board of Consultation, Massachusetts General Hospital.

and contributed many valuable publications to the literature. They included Thomas Fillibrown, Truman W. Brophy, Matthew W. Cryer, Thomas L. Gilmer, John S. Marshall and George Van Jugen Brown. The names of these men have been spoken in heartfelt gratitude by countless patients and their parents, because of the skillful correction of a variety of horrible deformities, or the repair of the ravages of cancer that had made these patients outcasts of society.

Oral surgery in the twentieth century became a recognized specialty of dentistry, included in the curriculum of all dental schools. That this surgical specialty was fostered and developed under the aegis of dentistry is natural when one considers that both the diagnosis and the treatment of oral disease require special knowledge of the anatomy and pathology of the teeth and jaws and that dentists are primarily concerned with the preservation and restoration of the proper functioning of the masticatory apparatus. Furthermore, medical schools have, in the past, shown very little interest in oral disease and have taken no responsibility for investigation and research to prevent such disease and maintain health and adequate function of the tissues involved.

Oral surgery has been defined by the American Board of Oral Surgery as the branch of dental practice that deals with the diagnosis, treatment, prescribing for or operating upon any disease, injury, malformation or deficiency of the human jaws or associated structures. The assignment of this field to dentistry in most states is backed by provisions of the dental law.² Thus, oral surgery is legalized and authenticated as a specialty of dentistry.

GRADUATE TRAINING

A very important step in the development of oral surgery is the establishment of postgraduate courses by some of the leading dental schools. Waldron^{4, 5} points out that acceptable programs for graduate training in oral surgery may show considerable variation in their plan of operation.

Some schools offer a graduate degree at the conclusion of the training period, though this is no more essential in oral surgery than it is in the program of graduate training in surgery and its various specialties. The first year of the training period should include training in basic science and study of fundamentals of clinical oral surgery. The remaining years should be devoted almost entirely to clinical and operative oral surgery.

Other schools, having accommodations for only a small number of students for the clinical work, may, through affiliations with other institutions, provide training under the guidance of accredited oral surgeons in various hospital centers.

Training may be offered by certain hospitals and clinics not associated with universities but approved for graduate training in surgery.

The course offered by the Graduate School of Medicine of the University of Pennsylvania is a good example of the high ideals set by its sponsors. It offers, in the first year, graduate training in advanced regional anatomy, bacteriology, immunology, physiology, biochemistry, pharmacology and special pathology, with autopsy assignments and participation in clinicopathological conferences. In addition, courses are offered in principles of surgery, medical physical diagnosis, anesthesiology, roentgenologic diagnosis and therapy, and experience in the clinical laboratory. Similar courses of one year's duration are given by Minnesota, Northwestern and other schools. The first year is followed by two years of internship either in the institutions teaching hospital or in another approved hospital, where the head of the department is a diplomate of the Board of Oral Surgery. The importance of appointing well trained and able teachers to hospital staffs is therefore paramount. According to the chairman of the Committee on Hospital Training of the American Board of Oral Surgery, a field survey committee will be appointed to evaluate the various training services in oral surgery and to give recognition to institutions that conform to the Board's minimum standard requirements that will make a trainee eligible for examination for certification.

RECENT ADVANCES

The more recent past contains a number of milestones that mark distinct developments in the field of oral surgery. These are local anesthesia, the perfection of which made it possible to perform all kinds of minor operations painlessly in a dentist's office, the denouncement of septic dentistry, which was the result of the endeavor to save teeth at all costs — many of these teeth so assiduously treated in the past were found to be infected and presented a source of great danger to the patient's general health, the influence of World War I with its trench warfare, which caused facial wounds and shattered jaws in enormous numbers, making a great demand on the skill of the comparatively few trained men of that time, the new field of traumatic jaw surgery of the postwar period, when civilian accidents became more frequent because of the rapidly increasing use of automobiles and airplanes, and the speeding up of industrial machines, the discovery of a fertile field consisting of a variety of asymptomatic jaw lesions revealed by the popularization of roentgenologic examination by both the physician and the dentist as part of a general examination, and finally the great discovery of chemotherapy and the use of antibiotics, which altered many procedures and eliminated many

dangers from oral surgical operations performed in an infected region

ANESTHESIOLOGY

It should be noted that two of the most important anesthetic agents, which are still the most popular and safest means of producing surgical narcosis, have been discovered by dentists. In addition, special technics have been developed by the latter to relieve pain by means of anesthesia and analgesia, not only for oral surgical operations but also for general dental procedures

Anesthesia in the Dental Office

Recently, the use of pentothal sodium, with or without nitrous oxide and oxygen, has been employed for short procedures by those who perform minor operations on ambulatory patients in offices.

The two most important topics in the use of general anesthetics are the question of anoxia, often resulting during the induction of nitrous oxide and oxygen anesthesia, and the question of the safety of giving general anesthetics, especially pentothal sodium, to ambulatory patients without adequate physical examination and preparation.

Nitrous oxide and oxygen The effects of anoxia and hypoxia, which are frequently produced by incorrect technic of induction and administration of nitrous oxide anesthesia that has a very narrow margin of oxygenation, were described by Courville.⁶ He pointed out that damage to the cerebral cortex is the penalty for insufficient oxygenation. It should be remembered, according to Kaye,⁷ that absence of cyanosis does not necessarily mean that no anoxemia is present. In anemic patients gross and dangerous suboxygenation may exist without signs of cyanosis since the oxygen-carrying capacity of the blood is reduced. In thyrotoxic subjects, too, the metabolic rate may be so high that oxygen lack exists even when the oxygen supply maintains normal color. Kaye points out that the absence of cyanosis is no guarantee of safety, and careful attention must be paid to assuring adequate oxygen administration in such cases. Schreiber,⁸ who reported 9 cases of severe cerebral damage and death, showed that anoxia may be brought about by the improper administration of any anesthetic. In 5 of his cases brain damage followed spinal anesthesia, and in one an asphyxial episode resulted in irreparable personality change when a tonsillectomy was performed under local anesthesia with a 0.5 per cent procaine solution. In 4 cases of prolonged anoxia, reported by Steegmann,⁹ in which brain damage was caused in 2, nitrous oxide was used. In the other 2 cases, avertin and cyclopropane were employed.

Seldin¹⁰ defends the use of nitrous oxide and oxygen and points out that there is no necessity for severe or prolonged anoxia to occur when nitrous oxide is correctly administered. His tabulation of

14,790 administrations shows that most patients will accept a surprisingly high percentage of oxygen with nitrous oxide without its interfering with maintenance of the third stage of anesthesia. In 85 per cent of the patients, anesthesia could be maintained with a minimum of 20 per cent oxygen. He states that the formula of 7 per cent oxygen and 93 per cent nitrous oxide used in the past is definitely wrong. McQuiston, Cullen and Cook¹¹ showed that any appreciable reduction of oxygen below 20 per cent may become extremely dangerous to the patient and that a reduction of oxygen below 12 or 13 per cent presents a great risk. If a patient cannot be adequately anesthetized with such a mixture, Arrowood¹² recommends that the nitrous oxide be supplemented with a more potent agent, such as ether, vinethene or pentothal.

The advantage of proper premedication has been stressed by Curran¹³ and Wiggin,¹⁴ as well as Arrowood.¹² The first recommends for ambulatory patients the short-acting secenal and nembutal, whereas Macintosh and Pratt¹⁵ suggest phenobarbital, 30 mg ($\frac{1}{2}$ gr) the night before the operation, 15 mg ($\frac{1}{4}$ gr) at breakfast time and 15 mg an hour before operation. Atropine, 0.4 mg ($\frac{1}{150}$ gr), Arrowood¹² points out, is very useful for drying up secretions that may hinder respiration.

Nasoendopharyngeal intubation is recommended by Cooper and Hill¹⁶ to avoid obstruction of the airway by retraction of the tongue, or by mucus, blood, pus or fractured teeth. A pack should be placed back into the mouth to avoid the aspiration of this material.

The need of a physical examination has been discussed by many writers. Macintosh and Pratt¹⁵ state, "We believe that a patient who does not volunteer a history of illness, and who is able to walk into the dental surgery, can be presumed fit enough to submit to a short dental anesthesia." Arrowood¹² points out that such an attitude courts disaster. Most of the modern writers on the subject agree. Arrowood recommends that a brief medical history be taken, and the questions asked should be planned to include the possibility of such maladies as allergic conditions, heart disease, especially of the myocardial type, and chronic pulmonary disease, especially with reference to vital capacity. Better still is a consultation with the patient's physician. This may yield important information regarding conditions, of which the patient is unaware, that may contraindicate the use of certain methods. Foldes¹⁷ points out that the history and physical examination should, in certain cases, be supplemented by various laboratory studies, and that special attention should be given patients with conditions that are adversely affected by the biochemical changes produced by the various anesthetic agents. Patients with diseases of the circulatory or respiratory systems and those with thyroid disease, kidney disease, liver disease, diabetes, allergic condi-

tions, blood dyscrasias and so forth should be hospitalized

In response to a questionnaire sent to the members of the American Society of Oral Surgeons, Seldin¹⁰ reports that 207 who replied had, during the preceding five years, administered approximately 2,429,148 anesthetics in their offices. Fifteen deaths were reported in this series. Nine deaths occurred from nitrous oxide for the following reasons: 2 patients had cardiac disease, 3 died of unknown cause, 1 patient with hypertension died eleven days later, 1 jumped out of the window during induction, 1 died of necrosis of the spinal cord, 1 died from "status lymphaticus" and sarcoma, 4 patients with cardiac diseases died during sodium pentothal anesthesia, 1 death occurred with novocain and pontocaine, and 1 additional death occurred under ethylene. Seven personality changes were reported, 6 were reversible, and 1 irreversible. According to this report, the death rate in these office administrations of anesthetic was 1/161,943, as compared with 1/1000 during administration in hospitals as reported by Waters and Gillespie¹⁸. It should be remembered, however, that the main reason for the comparative infrequency of fatal cases in office administration is the short duration of most operations performed on ambulatory patients. The comparative safety of a short anesthesia has been recognized by many writers. Macintosh and Pratt¹⁵ state that no operation of more than ten minutes' duration should be undertaken in the dental office. Gillespie¹⁹ places the limit at fifteen minutes. Since Chapman, Arrowood and Beecher²⁰ have demonstrated that it takes ten or fifteen minutes for full saturation with a given mixture of nitrous oxide, oxygen deprivation during these short procedures is not often sufficiently severe to be fatal, according to Arrowood¹².

To facilitate the induction of nitrous oxide and oxygen anesthesia, especially in obstreperous patients, or to achieve a deeper anesthesia without decreasing the percentage of oxygen, the admixture of trichlorethylene,²¹⁻²² vinethene²³ and ethyl ether is recommended, the last being the safest means of fortifying nitrous oxide anesthesia.²⁴ Premedication of ambulatory patients treated in the office is desirable but not practical since the delayed action of some of these drugs will endanger the patient's safety, especially if he is driving an automobile. Short-acting barbiturates are recommended such as seconal, nembutal and evicyl if the patient is kept under observation postoperatively and is taken home by an attendant.¹⁰⁻¹³⁻²⁴

Pentothal sodium. Intravenous anesthesia with pentothal sodium has been used in dentistry and oral surgery with increasing frequency and enthusiasm in recent years. Bullard,²⁵ in 1940, reported on 946 cases of anesthesia for exodontia and oral surgery with pentothal sodium. Olson²⁶ discussed a series of 8203 operations and stated

that he preferred pentothal to nitrous oxide and oxygen because of the almost total absence of the excitement stage and of postoperative nausea and vomiting. Other enthusiasts who advise its use for ambulatory patients are Archer²⁷ and Robert and Brown,²⁸ who recommend that pentothal be supplemented with oxygen.

Still others believe that it should be used as a synergist only. Seldin¹⁰ states, "This drug does not lend itself to unrestricted use as a principal anesthetic in prolonged oral surgery in the office because it is potentially dangerous if infection of the floor of the mouth or cellulitis of the neck is present." He recommends it for selected cases in combination with nitrous oxide and oxygen.

Many anesthesiologists approve of these methods if they are executed by a well trained person and if facilities are at hand to treat emergencies. Arrowood¹² believes that pentothal should be administered by a professional anesthetist only and not by the dentist himself. She points out that adequate premedication with atropine by depressing the parasympathetic system helps to protect against irritation of the larynx. Etsten and Himwich²⁹ state that the reflex irritability is markedly increased under light, and is not completely abolished even in deep pentothal anesthesia. Painful stimuli, especially from the region of the neck, may produce severe laryngeal spasm because the vagus nerve is not sufficiently depressed during this type of anesthesia to cause disappearance of the pharyngeal reflexes.³⁰ Spastic closure of the glottis, with extreme cyanosis, may result. Hubbell,³¹⁻³² however, who reported on 13,000 administrations, states that no complete laryngospasm occurred in his series of cases. Facilities for tracheal intubation and efficient suction should be immediately available if pentothal sodium is used. The importance of complete equipment is stressed by all the writers, but is especially emphasized by those who make anesthesia a specialty. Foldes¹⁷ states that the immediate availability of equipment necessary for resuscitation such as a suction apparatus, a laryngoscope and a variety of endotracheal tubes should always be on hand. There should also be equipment for the administration of oxygen under positive pressure and a sufficient number of competent assistants to aid in case of emergency.²⁵

According to Everson³³ pentothal anesthesia is contraindicated in patients with marked anemia, because of reduced oxygen-carrying capacity, hypertension (systolic blood pressure of 200 or more), hypotension (systolic blood pressure of 90 or less), since pentothal lowers the blood pressure by 8 to 40 per cent, impairment of respiratory function as caused by pulmonary secretions or metastatic disease and ankylosis of the jaw, as well as in very old and very young patients and those with coronary-artery disease, who should receive 100 per cent oxygen if this type of anesthesia is used.

dangers from oral surgical operations performed in an infected region

ANESTHESIOLOGY

It should be noted that two of the most important anesthetic agents, which are still the most popular and safest means of producing surgical narcosis, have been discovered by dentists. In addition, special technics have been developed by the latter to relieve pain by means of anesthesia and analgesia, not only for oral surgical operations but also for general dental procedures

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Nitrous oxide and oxygen The effects of anoxia and hypoxia, which are frequently produced by incorrect technic of induction and administration of nitrous oxide anesthesia that has a very narrow margin of oxygenation, were described by Courville.⁶ He pointed out that damage to the cerebral cortex is the penalty for insufficient oxygenation. It should be remembered, according to Kaye,⁷ that absence of cyanosis does not necessarily mean that no anoxemia is present. In anemic patients gross and dangerous suboxygenation may exist without signs of cyanosis since the oxygen-carrying capacity of the blood is reduced. In thyrotoxic subjects, too, the metabolic rate may be so high that oxygen lack exists even when the oxygen supply maintains normal color. Kaye points out that the absence of cyanosis is no guarantee of safety, and careful attention must be paid to assuring adequate oxygen administration in such cases. Schreiber,⁸ who reported 9 cases of severe cerebral damage and death, showed that anoxia may be brought about by the improper administration of any anesthetic. In 5 of his cases brain damage followed spinal anesthesia, and in one an asphyxial episode resulted in irreparable personality change when a tonsillectomy was performed under local anesthesia with a 0.5 per cent procaine solution. In 4 cases of prolonged anoxia, reported by Steegmann,⁹ in which brain damage was caused in 2, nitrous oxide was used. In the other 2 cases, avertin and cyclopropane were employed.

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oxygen and ether also may be recommended. Sodium pentothal is a vasodilator,⁴² and when it is combined with local anesthesia, bleeding can be controlled. Nerve block as well as infiltration will, in addition, allow the anesthetist to carry the patient through the operation with as little pentothal as possible.

(To be continued)

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Correction In the article by Dr Stanley E. Bradley entitled "Variations in Hepatic Blood Flow in Man during Health and Disease," which appeared in the March 24 issue of the *Journal*, the word "excretion" should be changed to "extraction" in the legend of Figure 5 and wherever it occurs in the text.

Local anesthesia The development of local anesthesia, especially conductive anesthesia (nerve block), with the discovery of novocain, has furnished the dentist a safe method by which he can perform operations in his office without resorting to general anesthesia and acting as his own anesthetist, avoiding the need of specially trained personnel and elaborate equipment. Unfortunately, this method made the undertaking of minor surgical procedures so easy from the anesthesia aspect that many inadequately trained dentists proclaimed themselves specialists in oral surgery.³⁴

However, local anesthesia has given the well trained oral surgeon an opportunity to perform dentoalveolar surgery safely on ambulatory patients without the preparation that is required for a general anesthetic. Performing minor procedures in the office under local anesthesia and using general anesthesia at a hospital for the more extensive operations, employing an expert anesthesiologist, is an ideal arrangement, though even with local anesthesia poor-risk patients should be hospitalized.³⁵ Greene³⁶ writes "regional anesthesia which is the method of choice should be urged on every patient in preference to general anesthesia if the patient is suitable for surgery in a conscious state."

The usual preparations to produce local anesthesia today contain procaine and epinephrine. More recently, monocaine with epinephrine has been recommended.³⁷ The same results are obtained with a 1 per cent solution of monocaine as with a 2 per cent solution of procaine.³⁸ In addition, monocaine has a synergistic action with epinephrine, and, therefore, smaller concentrations of this vasoconstrictor may be used (1:75000) than are required with procaine to which is added epinephrine 1:50000.

In oral surgery, epinephrine is considered indispensable. It aids in maintaining anesthesia long enough for the operation to be performed painlessly, and it produces hemostasis, which improves visibility of the field of operation. Many of the undesirable by-effects are due to the epinephrine rather than the procaine or monocaine since the use of epinephrine stimulates the myocardium, accelerates the heart rate and produces a rise in blood pressure. These have serious consequences in patients with cardiac complications³⁹ such as angina pectoris, coronary occlusion and severe hypertension or arteriosclerosis.

The combination of antibiotic agents and local anesthetic was recommended by Lundy and Osterberg,⁴⁰ who recommend the admixture of 250 units of penicillin per cubic centimeter of the anesthetic solution when it is injected into an infected region. They proved that penicillin does not interfere with anesthesia. Another suggestion was made by Copen,⁴¹ who advised premedication by comedication to overcome states of anxiety and fear. The inclusion of 25 mg of demerol hydrochloride with

monocaine and epinephrine is recommended, 125 mg for children. Others prefer premedication with secenal or pentobarbital sodium an hour before the administration.⁴⁴

Anesthesia for Oral Surgery in the Hospital

It is agreed by almost everyone that when a general anesthetic is necessary for a prolonged oral surgical operation, the patient should be hospitalized. I heartily concur with this recommendation. The obvious advantages are more careful physical checkup, preoperative correction of general disease, rest and control of food intake and hydration, proper premedication and preparation, maintenance of optimal conditions for the patient's metabolism in the postoperative period, and excellent postoperative general care and medication, not to speak of the proper use of antibiotics for the prevention or treatment of infections.

Endotracheal nitrous oxide, oxygen and ether anesthesia is by far the safest method for oral surgical operations.⁴²⁻⁴³ The Magill tube inserted through the nose leaves the oral cavity free, and the throat can be adequately packed to prevent aspiration of foreign material. Intubation minimizes leakage of the anesthetic agents. This type of anesthesia was highly approved of by Hunter⁴⁴ for maxillofacial surgery in the British Army in World War II.

Pentothal sodium with endotracheal nitrous oxide and oxygen is believed to be the anesthesia of choice by others.⁴⁴⁻⁴⁷ However, Wilson and Hiltmore⁴⁷ state, "The use of pentothal sodium alone is highly dangerous." They recommend "balanced anesthesia" of pentothal with nitrous oxide and oxygen. The induction is pleasant, less pentothal is required, the recovery is quicker, and there is complete freedom from straining and vomiting, which is important if intermaxillary fixation is used. Elliot and Arrowood⁴⁸ point out the advantages of pentothal sodium with tracheal intubation if diathermy procedures or electrocoagulation are contemplated in and around the head. Schultz and Guralnick,⁴⁹ besides combining nitrous oxide and oxygen with pentothal, believe that the addition of curare has advantages for more complicated cases in which maximum relaxation is essential during maintenance of a light plane of anesthesia. The combination of continuous pentothal sodium anesthesia with nerve block has been recommended by Thompson,⁵⁰ who reports on 100 consecutive cases. He points out that the method has many advantages, the most important of which is safety, since the amount of pentothal to carry the patient through the operation can be reduced to a minimum.

The combination of pentothal sodium with endotracheal nitrous oxide, oxygen and local anesthesia I find to be the ideal method when intravenous anesthesia is indicated. Its use with nitrous oxide,

mary adenocarcinoma of the second or third portion of the duodenum, which is rare but certainly occurs. We have all seen an occasional example of that disease. He may have had localized lymphoma of some sort, involving the same area, and a lymphoma at times is characterized by sharp localization of the tumor with infiltration of a given area of the gastrointestinal tract, but with no evidence of disease anywhere else.

This picture, to my mind, is not that of a duodenal ulcer. Peptic ulcers that are perfectly benign can occur in the third portion of the duodenum. They are not common, but many of them have been recognized — some at operation, and some by careful x-ray examination — but they do not give the x-ray picture that is described here, in my experience.

Benign tumor, of course, can involve this portion of the duodenum, but the appearance described here does not suggest benign tumor to me. A very remote possibility, as far as I can see, is that of localized enteritis. The usual site of this disease is the terminal ileum, occasionally, it involves the jejunum rather than the ileum, and rarely is it sharply localized in the upper small bowel. This is extremely rare but can happen and might involve the area considered as the duodenum. I do not believe it was regional enteritis, so-called, but I suppose that is a remote possibility. It is also possible that it was one of the various granulomatous processes we have to think of from time to time, but I have no reason to do any more than mention the possibility.

I do not know that there is any connection between the clarinet playing and the symptoms. Perhaps it was a fortuitous affair rather than an occupational hazard.

I would like to look at the x-ray films before finally trying to decide in my own mind what the diagnostic possibility is.

There is obviously enlargement of the duodenum.

DR JAMES J. McCORT: We have the films made on admission to this hospital. The esophagus and stomach do not show any abnormality. Beginning at the pylorus the duodenum shows a considerable widening all the way around to the junction of the third and fourth portions. From that point on the lumen shows severe narrowing for a distance of 0.7 cm. The constriction is gradual so that it is somewhat funnel shaped. A definite shelf defect cannot be made out. Within the narrowed segment a normal mucosal pattern is not seen, and there are fine serrations that indicate small ulcerations. The film taken three hours after the barium was administered shows considerable barium remaining in the dilated proximal two thirds of the duodenum.

DR JONES: These two spot films are the most important ones, are they not?

DR McCORT: Yes.

DR JONES: I think the only thing to do is to go out on the extreme end of the limb. I think the pa-

tient had an adenocarcinoma of the duodenum, with a secondary inflammatory process, I think it was not duodenal ulcer, and I believe it was not lymphoma. I am not familiar with the roentgenologic picture of lymphoma. I see no reason for thinking he had it except as a possibility to be included in differential diagnosis.

DR McCORT: Does the absence of a shelf have any significance?

DR JONES: Do you mean to imply that if he had a shelf, you would be more interested in the diagnosis of cancer? I would go with that. The question that I cannot answer is how frequently one can show a shelf with a cancer. I do not know that.

DR McCORT: I think it is frequently found.

DR JONES: I am sure of that. But is it in half, two thirds or a quarter of the cases?

DR McCORT: I would say a high percentage.

DR JONES: In other words, you are putting a little pressure on me to say that this was an inflammatory process. The presence of ulceration would fit in with that idea. I should say that ulcer was a possibility here, and against that idea is the complete absence of anything that can be called a focal lesion. I have already said adenocarcinoma of the duodenojejunal junction. I might as well stick to it. There was no disease anywhere else in the adjacent portion as far as I can find. It was localized, and the important thing was to take it out. I believe a surgical exploration is the only reasonable approach. If this was a jejunitis or duodenojejunitis, an inflammatory process per se, it has to be determined by biopsy. And I think biopsy of living tissue has to be made on this to establish finally what should be done. I am willing to admit that it was perhaps an inflammatory process, but I am not good enough to make the diagnosis.

DR RICHARD H. SWEET: There are two questions I would like to ask Dr. Jones. It looks to me from the x-ray studies here as if the lesion was actually in the jejunum and not in the duodenum. Would that influence you in favor of a diagnosis of regional enteritis or some such inflammatory lesion rather than a malignant neoplasm?

DR JONES: Yes, I think so, but as the x-ray description was given it was stated that it was in the third and fourth portions of the duodenum.

DR SWEET: Yes, but it looks like the jejunum to me.

DR McCORT: I cannot answer that exactly. I think it is on the proximal side of the ligament of Treitz.

DR SWEET: I would be surprised if it is.

DR GORDON A. DONALDSON: Dr. Jones should be commended for "sticking his neck out" before seeing the x-ray films. I have the impression that after he actually saw them he thought of hedging a little bit.

DR JONES: I left it "on the end of the limb."

DR DONALDSON: This was a very interesting and unusual problem. The record is misleading in that

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 35171

PRESENTATION OF CASE

A thirty-year-old clarinet player entered the hospital because of epigastric pain and vomiting.

Twenty months before admission the patient developed what he called "indigestion and dyspepsia." There was no vomiting, food intolerance or melena. These symptoms persisted for six to eight months and then ceased spontaneously except for sporadic attacks. Three months previous to admission the symptoms became severe. Six weeks before entry a Graham test at another hospital was negative. A gastrointestinal series showed marked dilatation of the descending and proximal transverse duodenum. There was an area of constriction in the mid-transverse duodenum that extended for a distance of about 8 cm. to the ligament of Treitz. The jejunum distally was normal. After four hours there was approximately 50 per cent retention of barium proximal to the constriction. Operation was advised but was refused. Epigastric pain and "heartburn" became severe. There was almost nightly vomiting—at 2 to 3 a.m.—of bile-stained material, which relieved the pain. He developed constipation but no melena. Fried or fatty foods promptly caused vomiting so that he restricted his diet to boiled foods, especially eggs and cereals.

The past and family histories were noncontributory.

Physical examination showed a short, obese man in no distress. The heart and lungs were normal. The abdomen was not tender, and there were no masses or tenderness. There was a maculopapular dermatitis confined to the region of the right axilla.

The temperature, pulse and respirations were normal. The blood pressure was 120 systolic, 80 diastolic.

The hemoglobin was 14 gm. The white-cell count was 7700. The urine sediment contained an occasional pus cell. The serum protein was 6.5 gm., the chloride 97 milliequiv. per liter and the nonprotein nitrogen 23 mg. per 100 cc. A gastric analysis showed no free hydrochloric acid in the fasting specimen, 5 units after alcoholic test meal and 44

units after histamine. A gastrointestinal series showed the duodenum to be rather severely dilated from the pylorus to about the junction of the second and third portions of the duodenum. At that point the barium column presented a rounded, blunted extremity, with marked delay in the passage of barium through this region. There was considerable reflux, and back-and-forth motion occurred between the stomach and duodenum. After some delay the barium entered the third portion of the duodenum, outlining a severely narrow segment of somewhat irregular caliber about 7 cm. long. Small projections suggested areas of ulceration. The distal portion of the narrowed area was of greater caliber than the remainder. The rest of the small bowel was not unusual. After four hours a large amount of barium was present in the dilated duodenum.

On the third hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. CHESTER M. JONES: On the third hospital day an operation was performed, which probably should have been done some weeks before. The obvious thing is that there was partial obstruction of the duodenum. That was obvious from the two sets of x-ray studies, and there is no evidence of any other disease, at least, on the basis of history, physical findings, laboratory data or x-ray examination. We are told that a cholecystogram was normal, and the x-ray film taken six weeks before admission to this hospital, in general, was entirely comparable to that taken a day or so after admission here. It would be interesting to know whether there was any occult blood in the stools. There is no statement about that. The patient had no anemia so I assume that he had not been bleeding to any great degree, but it would be interesting to know if there was enough erosion to cause occult blood.

DR. BENJAMIN CASTLEMAN: No stool examination is recorded.

DR. JONES: He was here three days, and the x-ray studies were done on the first and second days. I do not believe there would have been a stool examination. The symptoms were those of partial obstruction. As far as I can see, the question when he came in was primarily one of making a decision—namely, to operate or not to operate. Some partial obstruction was demonstrated in the duodenum, and operation seemed the only logical approach to the problem. That is the only important part of the picture. Exact diagnosis is interesting, but whatever diagnosis had been entertained preoperatively would have made very little difference in what one decided to do.

Regarding the possibilities underlying this partial obstruction, I am going to make what I call an intelligent guess, I hope. But it seems to me that the x-ray description can do nothing more than suggest certain possibilities. He may have had pri-

Physical examination revealed a well developed and well nourished boy in whom positive findings were limited to the left lower extremity. There were definite tenderness and moderate swelling over the medial epicondyle. There were no palpable bony masses. The joint line was not tender, and there was no fluid. Twenty centimeters above the patella, the left thigh measured 33 cm and the right 36 cm in circumference. The left leg showed a permanent flexion contracture of 25°, with further flexion to 140°. There was full range of flexion 0° to 150° on the right.

The temperature, pulse and respirations were normal.

The urine was normal. The blood hemoglobin was 15.5 gm, the white-cell count was 7000, with 66 per cent neutrophils. The blood cholesterol was 197 mg, the calcium 9.9 mg, the phosphorus 4.9 mg, and the phosphatase 5.9 units per 100 cc. The sedimentation rate was 19 mm per hour. The blood Hinton test was negative, as was a skin tuberculin test.

A roentgenogram of the left knee revealed an area of rarefaction, measuring 1.3 by 3.0 cm, in the region of the medial aspect of the femoral epiphysis and apparently crossing the epiphyseal line. Around the lesion was a sclerotic margin. The joint space appeared intact, and the articular surfaces were smooth. The lesion appeared to lie somewhat posteriorly. Roentgenograms of the spine, pelvis and upper extremities were normal. A subsequent scanogram confirmed the previous impression of a lesion in the medial aspect of the distal end of the femur with dissolution of bone on both sides of the epiphyseal line.

On the seventh hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR GRANTLEY W. TAYLOR: This patient presented an essentially negative examination except for what appeared to be a defect at the distal end of the femur. It seems as if the radiologist logically should present it instead of me, but I will be glad to look at the pictures and hazard a guess.

DR STANLEY M. WYMAN: The lesion, as described, lies in the medial portion of the distal end of the femur in the epiphysis and crosses very slightly the epiphyseal line. In the lateral aspect there is slight sclerosis about the margins of the defect, and the defect is sharply defined, although slightly irregular in contour. The oblique view shows the defect crossing the epiphyseal line somewhat better. There is no evidence of periosteal reaction. There is a soft-tissue mass.

The bones are not decalcified, and no other evidence of bone disease is apparent.

DR TAYLOR: We can be as elaborate or simple as we choose to be. We can start off by running through the infections — Brodie's abscess, osteo-

myelitis — or gumma. There are reasons against all these diagnoses, which I do not need to go into. The boy was not sick and never had been. There was no apparent disturbance of any vital functions, and the blood Hinton test was negative. The more recently described, perhaps infectious, process, called eosinophilic granuloma, should be alluded to just long enough to say that I do not know much about the disease. It is discovered from time to time, but chiefly by the pathologist. We operate on one of these lesions hoping to find out what it is, and the pathologist says that it is an eosinophilic granuloma. I do not know that it has characteristics in the radiogram that would do more than possibly raise that diagnosis. We have the cystic lesions of bone, — bone cysts occurring in the younger age groups in the shaft, in the metaphyses of the shaft, near the epiphyseal line, — and as the patients grow older the lesion moves closer to the middle of the bone, and the epiphysis grows away from it. We have such cysts as are present in parathyroid disease or fibrous dysplasia (Albright's syndrome). This bears no relation to that. Specific films of the other bones were taken to find out whether there was disease in the bones elsewhere, and they were normal. Other conditions that we ought to consider are xanthoma and Gaucher's disease. We need not do more than allude to them and pass them by.

We come very quickly to the conclusion that this must have been a tumor, and when one arrives at that point the decision must be made whether it was benign or malignant and, if malignant, whether primary in the femur or metastatic. The history is brief, but the history in a bone tumor, a large part of it, is frequently silent. It is not until symptoms begin to develop that one can date the onset. This boy had minor trauma, which drew attention to the knee, but the tumor may have existed for a long time before the trauma. There was impairment of function sufficient to cause atrophy of the thigh muscles but not bone atrophy. There is a little thickening in the soft tissues adjacent to the lesion, suggesting that perhaps with disturbed mechanics there was a little edema in a periosteal structure but no effusion in the joint. Boys of this age do not often have metastatic neoplasm. If they do, there is likely to be a primary focus, which betrays itself after careful investigation. Finally, metastatic disease would not present a picture comparable to this in that this bone lesion, whatever it was, had progressed in orderly fashion, with a zone of concentration of bone, suggesting an encapsulating process. That zone of encapsulation would work very much against a primary malignant lesion of the bone, such as osteogenic sarcoma, Ewing's tumor or lymphoma.

It seems to me that we come rapidly to the conclusion that this was a benign tumor involving this part of the bone, and then we can recapitulate the common types of bone tumor. One of the most re-

one might picture the patient as being quite depleted. As a matter of fact, he was a healthy, slightly obese, well nourished young man. He had had three sets of radiologic studies, but they were never able to demonstrate the involved area here. It was not until he got to the Baker Memorial that it was possible to displace the stomach upward and the small bowel laterally so that this area showed up. The important point that Dr. Jones brought out was that he had to be explored for duodenal ob-



FIGURE 1

struction. I shall simply point out that at exploration Dr. Allen found this mass to be more extensive than shown by x-ray examination. It extended for 10 cm into the jejunum and 10 cm into the duodenum, centering at the ligament of Treitz. We thought first of carcinoma and rather than any side-tracking procedure, a resection and duodeno-jejunosomy posterior to the transverse colon were done. Examination of the remainder of the small bowel revealed it to be normal down to the terminal ileum.

CLINICAL DIAGNOSIS

Regional enteritis

DR. JONES'S DIAGNOSIS

Adenocarcinoma of duodenojejunal junction

ANATOMICAL DIAGNOSIS

Regional enteritis of duodenum

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: This is a portion of the resected specimen showing the lesion at one end (Fig. 1). I

do not think it is 20 cm in length. Allowing for some contraction after removal, I do not believe the entire lesion measures more than 10 cm. It appears to be entirely within the duodenum. It will be noticed that the wall is very thick and edematous, and the mucosa in the lesion is ulcerated in several places. The intervening mucosa is raised in verrucous formation. The appearance in gross corresponds to what we see in the ileum in regional enteritis. Microscopically, in the regions of the ulcerations there is much purulent exudate. Deeper in the wall is granulation tissue and a more chronic inflammatory reaction. The nerves in the wall of the bowel seemed very prominent with the infiltrate surrounding them, and I wonder if the pain may not in some way have been related to the severe infiltration around the nerves in the muscle layer. The serosa also shows an inflammatory reaction. As far as I can make out, this is a nonspecific reaction. There are a few areas that show epithelioid cells and an occasional giant cell, which is seen in regional enteritis. I do not believe it is tuberculosis. We have some material in a guinea pig, but it is still too early to find out. If this was regional enteritis, it is the first time we have seen it localized to the duodenum. I believe we have had one case in which the disease spread from some other region to the duodenum. The regional lymph nodes were chronically inflamed and did not show any of the granulomas sometimes seen in regional enteritis. I suppose this film demonstrates the string sign seen in regional enteritis.

DR. JONES: Yes, but that could be an infiltrating process of any sort, and if it were a lymphoma, ulceration could still occur. As I have already stated, a few cases have been reported of enteritis involving this area, but it is most unusual. Resection, of course, was the obvious move.

DR. CASTLEMAN: The patient was discharged home, apparently well.

CASE 35172

PRESENTATION OF CASE

A thirteen-year-old boy was admitted to the hospital because of stiffness in the left knee.

Four months before admission the patient injured the medial aspect of the left knee while playing football. There was no swelling or ecchymosis, and the injury was not severe enough to cause him to leave the game. One month later he noted the onset of stiffness and inability to extend the leg fully. There was no pain at rest or at night. Pain located over the left medial epicondyle became present when he first started walking but after he had gone 100 yards or so it disappeared.

The past and family histories were essentially noncontributory.

Physical examination revealed a well developed and well nourished boy in whom positive findings were limited to the left lower extremity. There were definite tenderness and moderate swelling over the medial epicondyle. There were no palpable bony masses. The joint line was not tender, and there was no fluid. Twenty centimeters above the patella, the left thigh measured 33 cm and the right 36 cm in circumference. The left leg showed a permanent flexion contracture of 25°, with further flexion to 140°. There was full range of flexion 0° to 150° on the right.

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DIFFERENTIAL DIAGNOSIS

DR GRANTLEY W. TAYLOR: This patient presented an essentially negative examination except for what appeared to be a defect at the distal end of the femur. It seems as if the radiologist logically should present it instead of me, but I will be glad to look at the pictures and hazard a guess.

DR STANLEY M. WYMAN: The lesion, as described, lies in the medial portion of the distal end of the femur in the epiphysis and crosses very slightly the epiphyseal line. In the lateral aspect there is slight sclerosis about the margins of the defect, and the defect is sharply defined, although slightly irregular in contour. The oblique view shows the defect crossing the epiphyseal line somewhat better. There is no evidence of periosteal reaction. There is a soft-tissue mass.

The bones are not decalcified, and no other evidence of bone disease is apparent.

DR TAYLOR: We can be as elaborate or simple as we choose to be. We can start off by running through the infections — Brodie's abscess, osteo-

myelitis — or gumma. There are reasons against all these diagnoses, which I do not need to go into. The boy was not sick and never had been. There was no apparent disturbance of any vital functions, and the blood Hinton test was negative. The more recently described, perhaps infectious, process, called eosinophilic granuloma, should be alluded to just long enough to say that I do not know much about the disease. It is discovered from time to time, but chiefly by the pathologist. We operate on one of these lesions hoping to find out what it is, and the pathologist says that it is an eosinophilic granuloma. I do not know that it has characteristics in the radiogram that would do more than possibly raise that diagnosis. We have the cystic lesions of bone, — bone cysts occurring in the younger age groups in the shaft, in the metaphyses of the shaft, near the epiphyseal line, — and as the patients grow older the lesion moves closer to the middle of the bone, and the epiphysis grows away from it. We have such cysts as are present in parathyroid disease or fibrous dysplasia (Albright's syndrome). This bears no relation to that. Specific films of the other bones were taken to find out whether there was disease in the bones elsewhere, and they were normal. Other conditions that we ought to consider are xanthoma and Gaucher's disease. We need not do more than allude to them and pass them by.

We come very quickly to the conclusion that this must have been a tumor, and when one arrives at that point the decision must be made whether it was benign or malignant and, if malignant, whether primary in the femur or metastatic. The history is brief, but the history in a bone tumor, a large part of it, is frequently silent. It is not until symptoms begin to develop that one can date the onset. This boy had minor trauma, which drew attention to the knee, but the tumor may have existed for a long time before the trauma. There was impairment of function sufficient to cause atrophy of the thigh muscles but not bone atrophy. There is a little thickening in the soft tissues adjacent to the lesion, suggesting that perhaps with disturbed mechanics there was a little edema in a periosteal structure but no effusion in the joint. Boys of this age do not often have metastatic neoplasm. If they do, there is likely to be a primary focus, which betrays itself after careful investigation. Finally, metastatic disease would not present a picture comparable to this in that this bone lesion, whatever it was, had progressed in orderly fashion, with a zone of concentration of bone, suggesting an encapsulating process. That zone of encapsulation would work very much against a primary malignant lesion of the bone, such as osteogenic sarcoma, Ewing's tumor or lymphoma.

It seems to me that we come rapidly to the conclusion that this was a benign tumor involving this part of the bone, and then we can recapitulate the common types of bone tumor. One of the most re-

cent accretions to this category is osteoid osteoma I do not recall ever seeing that condition in the epiphyses. Characteristically, there is a punched-out area of bone, with some condensation around it, and invariably a careful search discloses a small condensation in the center, a little grainlike focus that is apparently the crux of the problem and the removal of which is accompanied by relief of symptoms. Benign cysts I referred to earlier as being in the shaft of the bone. The giant-cell tumor, it seems to me, must be seriously considered. Giant-cell tumors, arranged in relation to the epiphyses of the long bone, grow over into all the nooks and crannies of the joint surface, leaving a thin rim of bone. They grow by expansion and usually preserve an intact overlying periosteum for a long period. The x-ray appearance of giant-cell tumor is apt to show more trabeculation, which helps to identify it in the roentgenogram. Chondromas, not the osteochondromatosis but simple chondromas, are likely to occur in relation to cartilaginous plate, such as epiphyseal plate. They are much more common in the small bones of the hands and feet, and occasionally occur in the ends of the long bones, and also in the ribs and in the vertebrae. It seems to me that we have to consider that seriously. The characteristic arrangement is apt to show coarse trabeculation of bone as supporting it. I have never seen hemangiomas in this location, which does not mean they may not occur. They are much more common in the small or compact bones like the vertebrae. The growth is progressive and expansive and does not, as a rule, start a zone of protective reaction ahead of the tumor. Finally, the nonossifying fibroma must be considered — fibroma of the bone, with which this picture is entirely consistent. I think, from the point of view of the surgeon, one arrives at the conclusion that this was a benign tumor of bone and leaves to his colleague, the pathologist, the decision exactly what sort of tumor it is. Sometimes the radiologists will tell us unequivocally that this is thus and so — a tumor. I believe that is an esoteric art that they acquire and are incapable of communicating to me, although I strive to follow them by implication and inference from the films. I think this was a benign tumor of bone, probably fibroma or chondroma.

DR TRACY B MALLORY: Have you any comment on the x-ray films, Dr Wyman?

DR WYMAN: I should say that Dr Taylor has done a great deal better than his x-ray colleagues in this diagnosis. We thought of chronic infection, benign tumor and eosinophilic granuloma.

CLINICAL DIAGNOSIS

Bone cyst

DR TAYLOR'S DIAGNOSIS

Benign tumor of bone fibroma or chondroma

ANATOMICAL DIAGNOSIS

Benign chondroblastoma of femur

PATHOLOGICAL DISCUSSION

DR MALLORY: I think this is an example of a type of tumor that was first clearly recognized by Dr Codman¹ of the staff of this hospital, some eighteen years ago, which he called at that time chondromatous giant-cell tumor of bone and noted that it most commonly occurred in the head of the humerus. He was able to discover 8 cases in that area, many of which had been erroneously described as osteogenic sarcoma. More recently, Jaffe and Lichtenstein² have found that tumors of this type occur in other bones besides the humerus, perhaps almost with equal frequency. They disagreed with Dr Codman in his interpretation that this was an atypical form of giant-cell tumor and gave it the name of benign chondroblastoma of bone. They pointed out a number of characteristic features that it is always seen in young persons, usually between thirteen and twenty years of age — this boy just falls in at the lower end of their age scale — that there is frequently, though not invariably, a history of trauma as there was here, and that the lesion is always found in the epiphysis, very close to the epiphyseal line, although in about a quarter of the cases it crosses the epiphyseal line as this one did. From the x-ray point of view it is characteristically surrounded by a dense line of condensation of bone, as in the case under discussion. Histologically, the tumor simulates benign giant-cell tumor, but there are always certain atypical features: one is that the number of large giant cells is frequently slight compared with the typical giant-cell tumor, that the tumor cells tend to lay down a slightly basophilic, intercellular matrix, which faintly suggests cartilage. Calcification develops focally in this matrix, and the neighboring tumor cells become necrotic. Finally, the necrotic focus heals by organization with a peculiar type of hyaline fibrous tissue, which again resembles poorly formed cartilage. This particular tumor shows all these various features. Whether or not Jaffe and Lichtenstein are correct in their interpretation of the lesion as a chondroblastoma, they have described a clinical and pathological entity. This case is beyond doubt a characteristic example.

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"CAULDRON BUBBLE"

PROPOSED legislation bearing on the extension of medical services has been augmented by the introduction in Congress on March 30 of S1456, the "Voluntary Health Insurance Bill." This bill, which was introduced by Senator Lister Hill of Alabama, co-author of the familiar Hill-Burton Act, bore the additional signatures of Senators George D. Aiken of Vermont, O'Connor of Maryland, Withers of Kentucky and Morse of Oregon.

Patterned to some degree after the Hospital Survey and Construction Act, the Voluntary Health Insurance Bill seeks to employ the same methods in financing hospital and medical care that the Hill-Burton Act uses in the construction of new hospitals and health centers.

The purpose of the bill is "to make a high quality of hospital and medical care available to all persons in each state by (a) strengthening and co-ordinating existing health resources within the State, (b) encouraging and stimulating voluntary enrollment in prepayment plans for hospital and medical care, with emphasis on employer participation and on making such protection available to persons in rural areas, and (c) providing protection to persons financially unable to pay all or part of subscription charges for prepayment of hospital and medical care." The services to be rendered are to be furnished in a hospital, not in excess of sixty days in any year.

The financing of the Plan would be similar to that of the Hospital Survey and Construction Act of 1946, through federal grants and a variable percentage of funds from state and local sources, giving a greater percentage of aid to low-income states.

It is important to note that the program would be entirely in the hands of the state agency acting in consultation with a state hospital and medical-care council, and regional hospital and medical-care authorities within the state. This method of administration is already in effect in many states to carry out the provisions of the Hill-Burton Act.

Persons unable to pay the costs of medical and hospital care would have it made available through Government-supported membership in nonprofit, prepayment health-insurance programs. Since these recipients would not be identified as the beneficiaries of governmental assistance, their anonymity would be safeguarded, they would be spared the "indignity of a means test."

The Voluntary Health Insurance Bill, whether or not it is enacted, represents a relatively conservative step down the road of socialization to which the whole world is committed. Such a step would have been bitterly opposed by all conservative elements ten years ago, and with reason. Today it is viewed with comparative equanimity. The times, the customs, the viewpoints of people change. The attitude of critics who today decry the conservatism of a decade ago shows in itself a reluctance to recognize progress in other camps than their own.

Dr. Channing Frothingham, of Boston, chairman of the Committee for the Nation's Health and

cent accretions to this category is osteoid osteoma. I do not recall ever seeing that condition in the epiphyses. Characteristically, there is a punched-out area of bone, with some condensation around it, and invariably a careful search discloses a small condensation in the center, a little grainlike focus that is apparently the crux of the problem and the removal of which is accompanied by relief of symptoms. Benign cysts I referred to earlier as being in the shaft of the bone. The giant-cell tumor, it seems to me, must be seriously considered. Giant-cell tumors, arranged in relation to the epiphyses of the long bone, grow over into all the nooks and crannies of the joint surface, leaving a thin rim of bone. They grow by expansion and usually preserve an intact overlying periosteum for a long period. The x-ray appearance of giant-cell tumor is apt to show more trabeculation, which helps to identify it in the roentgenogram. Chondromas, not the osteochondromatosis but simple chondromas, are likely to occur in relation to cartilaginous plate, such as epiphyseal plate. They are much more common in the small bones of the hands and feet, and occasionally occur in the ends of the long bones, and also in the ribs and in the vertebrae. It seems to me that we have to consider that seriously. The characteristic arrangement is apt to show coarse trabeculation of bone as supporting it. I have never seen hemangiomas in this location, which does not mean they may not occur. They are much more common in the small or compact bones like the vertebrae. The growth is progressive and expansive and does not, as a rule, start a zone of protective reaction ahead of the tumor. Finally, the nonossifying fibroma must be considered — fibroma of the bone, with which this picture is entirely consistent. I think, from the point of view of the surgeon, one arrives at the conclusion that this was a benign tumor of bone and leaves to his colleague, the pathologist, the decision exactly what sort of tumor it is. Sometimes the radiologists will tell us unequivocally that this is thus and so — a tumor. I believe that is an esoteric art that they acquire and are incapable of communicating to me, although I strive to follow them by implication and inference from the films. I think this was a benign tumor of bone, probably fibroma or chondroma.

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JOSEPH VON MERING (1849-1949)

FEBRUARY 28 marked the hundredth birthday anniversary of Joseph von Mering. He belonged to that group of German clinicians who like Naunyn, F von Müller and Minkowski were responsible to a high degree for the great progress in experimental pathology at the end of the nineteenth and the beginning of the twentieth century. He had an excellent medical education. Hoppe-Seyler introduced him to biochemistry, Ludwig was his teacher in physiology. He worked with Goltz on neurologic problems. He was Frerich's assistant in the medical clinic of the University of Berlin. Mering became privatdozent and assistant professor at Strassburg under Kussmaul and later director of the medical polyclinic and medical clinic of the university in Halle. There he died in 1908. His knowledge of medicine was remarkable. He taught pharmacology, legal medicine, larvngology and internal medicine. Twice he was offered a chair in pharmacology and was also nominated by the faculty of the University of Vienna as successor of Stricker in the post of professor of experimental pathology.

Mering's scientific work includes three main spheres: the investigations on diabetes mellitus, the connection between chemical constitution and effect of hypnotic drugs and the conditions of absorption in the stomach. In 1886 he discovered the phlorhizin diabetes, and in 1889 he published with Minkowski the first paper on experimental pancreatic diabetes. His experimental work on the constitution and effect of narcotics started with studies on chloral hydrate and was crowned with the discovery of veronal, which he made when working with Emil Fischer. His investigations on the physiology of absorption from the intestine yielded fundamental knowledge about the absorption of water, sugar, dextrin and peptones from the stomach.

In his textbook of internal medicine, which he edited with Krehl, he tried for the first time to apply the principles of the great encyclopedic handbooks to a short textbook, and he did it successfully, as the great number of editions of this textbook proves.

"EEG JOURNAL"

IN FEBRUARY of this year the medical journals of the world had the opportunity and the privilege of welcoming into their austere ranks the newest comer of them all — *Electroencephalography and Clinical Neurophysiology*. The official organ of the International Federation of EEG Societies, this quarterly international journal would represent almost the ultimate degree in specialization were it not for its broader scope. This breadth of interest allows it to include 'any aspect of the physiology of the nervous system or neuromuscular system which may contribute to progress in our understanding of the neural basis of behaviour'.

As stated at its masthead its purpose is threefold

to provide an official organ for the various EEG Societies being established throughout the world, to bring together in one publication selected studies of merit in the growing field of neurophysiology as applied to the understanding of human behaviour, both normal and abnormal, and to foster international co-operation and understanding among scientists with these common interests.

Any newcomer to the journalistic field — as well as the old-timers — must see to it that the saddle girth is tightened and the stirrups adjusted, for there may be a rough ride ahead. "The EEG Journal," however, has been launched under good auspices and with excellent backing. The editor is Herbert H. Jasper, of Montreal, the co-editor, W. Grey Walter, of Bristol, England, and the managing editor, Robert S. Schwab, of Boston. The editorial board is representative of the civilized world. The publication office is in the charge of Dr. Schwab at the Massachusetts General Hospital.

The first number is concerned largely with a symposium on the physiologic basis of epileptic discharge delivered at the annual meeting of the American Electroencephalographic Society in June, 1948. May success crown its continuing efforts!

a former president of the Massachusetts Medical Society, calls the Hill bill, according to *Washington Report on the Medical Sciences*, "either a fraud on the American people or a proposal to appropriate billions of dollars out of the Treasury without any assurance that it will provide adequate medical care."

Even as this issue of the *Journal* goes to press, Senators Taft of Ohio, Smith of New Jersey and Donnell of Missouri have introduced their own national health bill. This also calls for federal aid to states, instead of compulsory insurance.

It is anticipated that the next few months will witness considerable controversy over the Nation's health.

BOSTON LYING-IN HOSPITAL

THE function of the voluntary teaching hospital in making available special services that usually accompany the more recent advances in medical knowledge and technics has always been considered one of the major contributions that large medical centers can make to improve medical care. In these times when there is a great desire to change the mode of medical practice, it is well to examine the extent to which the teaching hospital is able to contribute to the medical services of a community, for one might question whether these services have been completely utilized under the present system. The availability of the services is often not adequately appreciated by either the practicing physicians or the neighboring hospitals. This idea is especially prevalent regarding the specialty hospital, for in the minds of the practicing physicians these institutions are capable of rendering only one type of medical service. Frequently, such attitudes are due to the fact that the teaching hospitals have not informed the medical community of the character and scope of the services that they have to offer.

A more co-operative effort between institutions in attempting to solve complicated medical problems should produce a wider distribution of medical care and should provide additional opportunity for the accumulation and dissemination of medical knowledge. The branch of medicine concerned with maternal and child health affords an excellent opportunity for such a co-operative effort.

During the past two decades a gratifying reduction in maternal mortality and morbidity has occurred,

with a parallel improvement in the mortality rate in the newborn. This result has been due in large measure to an increase in hospital facilities and in trained personnel. This has been reflected by an improved quality of prenatal care and the provision of the proper hospital surroundings to cope with the complicated obstetric emergency. These services must continue. However, a further reduction of maternal and fetal mortality and morbidity will depend on a more careful screening of the obstetric patient with chronic problems and to anticipate and provide the specialized care that she and her infant may demand. It is obvious that with this general improvement in the maternal mortality rate the chronic patient will contribute a greater percentage of the mortality of the future. In addition, many patients with other conditions such as infertility, premature labor, abortion, Rh sensitivity and certain gynecologic disorders related to pregnancy and those with possible labor dystocia should have available the benefits of specialized diagnostic and therapeutic aids to ensure the best in present-day medical care.

The Boston Lying-in Hospital has over the years developed special clinics devoted to these problems. Clinics are available for the supervision of the cardiac, diabetic, urologic and toxemic patient, as well as those with possible labor dystocia. Recent figures released by the Children's Bureau have shown that this hospital has developed a method of care that has produced the lowest mortality among premature infants of any large maternity hospital in the country. In this institution replacement transfusions for the treatment of infants with erythroblastosis was first carried out in New England.

Believing that the voluntary teaching hospital has an even greater future in aiding the distribution of medical care and knowledge, this institution has recently completed a successful campaign to obtain the funds necessary to create facilities for the provision of consultation services as well as additional space to be devoted for teaching and research. It is hoped that physicians throughout New England will utilize these consultation services for the benefit of their patients. It is believed that only in this manner can any teaching institution such as the Boston Lying-in Hospital fulfill its obligations to the medical welfare of the area that it serves.

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MASSACHUSETTS MEDICAL SOCIETY

COMMENT

DEATHS

COBB — Oliver W Cobb, M D, of Northampton, died on April 6. He was in his ninety-first year.

Dr Cobb received his degree from University of Virginia Department of Medicine in 1897. He was a former president of Hampshire District Medical Society, counselor of the Massachusetts Medical Society and a member of the medical staff of Cooley-Dickinson Hospital. He was an affiliate fellow of the American Medical Association.

Two sons, five grandchildren and two great-grandchildren survive.

DRAKE — Richard A Drake, M D, of Marshfield, died on April 8. He was in his seventy-first year.

Dr Drake received his degree from Harvard Medical School in 1902. He was a member of the staff of Lawrence Memorial Hospital and was formerly city physician in Medford.

His widow and three daughters survive.

ROE — John C Roe, M D, of Pittsfield, died on March 13. He was in his sixtieth year.

Dr Roe received his degree from Georgetown University School of Medicine in 1915. He was chief of the surgical staff at Pittsfield Hospital and was formerly associate medical examiner of Berkshire District. He was a fellow of the American College of Surgeons and American Medical Association and was a member of the staffs of St Luke's and Hillcrest hospitals in Pittsfield, Fairview Hospital in Great Barrington and W B Plunkett Memorial Hospital in Adams.

His widow, four sons and three daughters survive.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATH

ADAMS — Charles W Adams, M D, of Franklin, died on March 12. He was in his eighty-sixth year.

Dr Adams received his degree from Boston University School of Medicine in 1884. He was one of the founders of the Franklin Hospital and had served on the State Medical Board and Franklin Board of Health.

A son, two grandchildren and three great-grandchildren survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR MARCH, 1949

RÉSUMÉ

DISEASE	MARCH 1949	MARCH 1948	SEVEN-YEAR MEDIAN
Chancroid	7	4	2*
Chicken pox	4026	2405	1793
Diphtheria	41	21	20
Dog bite	964	864	790
Dysentery bacillary	4	9	9
German measles	892	119	316
Gonorrhea	274	215	327
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	3	1	2*
Malaria	0	7	8
Measles	6550	4205	3245
Meningitis, meningococcal	8	6	21
Meningitis, Pfeiffer-bacillus	0	4	4
Meningitis, pneumococcal	4	2	2
Meningitis staphylococcal	0	1	0
Meningitis streptococcal	0	5	7
Meningitis undetermined	1788	2522	1575
Mumps	0	0	2
Polio-myelitis	0	4	8
Salmonellosis	1215	703	1457
Scarlet fever	218	226	443
Syphilis	180	227	230
Tuberculosis pulmonary	12	25	20
Tuberculosis other forms	0	1	1
Typhoid fever	7	4	4
Undulant fever	319	241	645
Whooping cough			

*Five-year median

Diseases above the seven-year median were chicken pox, diphtheria, German measles, measles, mumps and undulant fever.

Diseases below the seven-year median were bacillary dysentery, meningitis (all types), salmonellosis, scarlet fever and whooping cough.

For the sixth consecutive month chicken pox was at the highest level ever reported. German measles was at the highest it has been since the epidemic year 1943. The incidence of measles was the highest in March except for the record year 1934, when there were 9891 cases during the month. Only once since 1934 has diphtheria been higher for the month of March.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Anthrax was reported from Newton, 1, Somerville, 1, total, 2.

Diphtheria was reported from Billerica, 1, Boston, 23, Brookline, 1, Chelsea, 1, Danvers, 2, East Brookfield, 5, Everett, 1, Fall River, 1, Malden, 1, Newton, 1, Revere, 1, Rockport, 1, Somerville, 1, Spencer, 1, total, 41.

Dysentery, amebic, was reported from Danvers, 1, total, 1. Dysentery, bacillary, was reported from Wrentham, 4, total, 4.

Encephalitis, infectious, was reported from Brockton, 1, Quincy, 2, total, 3.

Infectious hepatitis was reported from Boston, 2, Springfield, 1, Williamstown, 1, Worcester, 1, Wrentham, 3, total, 8.

Lymphocytic choriomeningitis was reported from Cambridge, 1, total, 1.

Meningitis, meningococcal, was reported from Cambridge, 2, Everett, 1, Fall River, 2, Hadley, 1, Lawrence, 1, Palmer, 1, total, 8.

Meningitis, pneumococcal, was reported from Lawrence, 1, Quincy, 1, Salem, 1, Worcester, 1, total, 4.

Meningitis, undetermined, was reported from Fall River, 1, Hanover, 1, Northbridge, 1, Randolph, 1, total, 4.

Salmonellosis was reported from Wellesley, 2, total, 2.

Septic sore throat was reported from Boston, 8, Lynn, 2, Swampscott, 1, Taunton, 1, Worcester, 8, total, 20.

Trichinosis was reported from Boston, 3, Cambridge, 1, Quincy, 1, Westwood, 1, total, 6.

Undulant fever was reported from Bridgewater, 1, Malden, 1, Newton, 1, Pembroke, 1, Sandwich, 1, Swansea, 1, Wilmington, 1, total, 7.

MISCELLANY

WOMAN'S AUXILIARY, SUFFOLK DISTRICT

At its annual meeting on April 7, the Woman's Auxiliary of the Suffolk District Medical Society elected the following officers and committee chairmen for 1949-1950: president, Mrs Joseph Garland, vice-president, Mrs Roger I Lee, secretary, Mrs J Martin Woodall, treasurer, Mrs Charles G Shedd, director for one year, Mrs Harvey A Kelly, director for two years, Mrs Donald Munro, and director for three years, Mrs Thomas H Lanman. The chairmen of the various committees are Mrs David J Calcechio (membership), Mrs Raymond A Dillon (program), Mrs Howard F Root (legislation), Mrs James P O'Hare (health education), Mrs Albert A Horner (public relations) and Mrs Merrill C Sosman (hospitality).

CORRESPONDENCE

CONSULTATIVE SERVICE IN OBSTETRICS

To the Editor: The following letter, which is being sent to the chief of staff of those community hospitals within a reasonable radius of Boston that have no formal obstetric service, is self-explanatory.

Dear Dr —

It is the desire of the Boston Lying in Hospital to increase its medical service to physicians and their obstetric patients throughout New England. This letter is concerned with the possible need for and the desirability of establishing free medical consultation service at the Boston Lying in Hospital for the complicated obstetric case, should the attending physician so desire it. We are now

in the process of improving the hospital's facilities. Special attention is being given to the enlarging of the outpatient department. This will allow for more adequate housing of the cardiac, diabetic, urologic, toxic, dystocia and Rh clinics, as well as many ancillary services. These clinics will be supervised by physicians who are eminent in their fields, and many are no doubt familiar to you. Naturally, since the hospital is a teaching institution, the resident staff will also be closely associated with the care of patients in these clinics.

To enhance the educational value of the institution to the community, we thought that members of your staff might be interested in the treatment of the complicated cases as they occur here at the hospital. It might be desirable to hold meetings from time to time at the hospital when certain obstetric topics would be discussed or a periodic review of the treatment of the complicated cases could be presented. We wish you would question your staff regarding the need for such consultation service and meetings. We would appreciate your opinion on these matters.

DUNCAN E. REID, M.D.
Obstetrician-in-Chief

Boston Living-in Hospital

BOOK REVIEW

The Physicians of Essex County. By Russell L. Jackson. With a foreword by Harold Bowditch, M.D. 8°, cloth, 152 pp., with 12 illustrations and frontispiece. Salem, Massachusetts: The Essex Institute, 1948.

In the Essex Institute in Salem, Massachusetts, is a vast collection of material on doctors who were born in or who subsequently lived in Essex County. Much has found its way into print in the last eighty-four years in the Essex Institute Historical Collections, but a greater amount remains unpublished in papers, diaries and memoirs. The present director of the Institute has cast a wide net to catch the vital facts about the County physicians, many without medical degrees, others ministers of the Gospel, who practiced their art from the early seventeenth century to 1840. The list is a long one, has been carefully compiled, with appropriate references to sources of information. Most of the notices are short, — only a few lines, — but others of more famous personages comprise even a page or more. A few illustrations accompany the text, unfortunately without reference to their source. The brief biographic notes are listed alphabetically, but there is also an extensive index. Mr. Jackson has produced a sound, biographic study, gracefully acknowledged in the Introduction by Dr. Harold Bowditch, long a devoted student of medical history.

NOTICES

ANNOUNCEMENTS

Dr. Charles Djerf announces the opening of his office at 1200 Hancock Street, Quincy, for the practice of pediatrics.

Dr. Walter J. McDonough announces the opening of his office for the practice of diseases of the skin at 270 Commonwealth Avenue, Boston.

JOHN T. BOTTOMLEY MEDICAL SOCIETY

A meeting of the John T. Bottomley Medical Society will be held in the auditorium of the Carney Hospital on May 2 from 11 30 a.m. to 1-00 p.m. Dr. Herbert G. Finn will speak on the subject "Treatment of Cancer of the Skin." Drs. Morris Shapiro and Robert Grandfield will lead the discussion.

Physicians and medical students are cordially invited.

SUFFOLK DISTRICT MEDICAL SOCIETY

The annual meeting of the Suffolk District Medical Society will be held in Ware Hall, Boston Medical Library, 8 Fenway, Boston, on Wednesday, May 4, at 4 30 p.m.

There will be a meeting of the councilors of Suffolk District Medical Society on the same day and place at 3 30 p.m.

AGENDA

- Call to order by the President
- Reports of committees
- Consideration of an annual assessment
- Unfinished business
- Blue Shield and Blue Cross Affairs
Charles G. Hayden, M.D.
- Report of Massachusetts Medical Society Affairs
H. Quimby Gallupe, M.D.
- Such other business as may properly be brought before the Society
- Adjournment

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children, will be held in the classroom of the Nurses' Residence on Thursday, May 5, at 7 15 p.m. Dr. Edward L. Young will speak on the subject "Liver Abscesses as Complication of Biliary Surgery." Dr. Gullh. Lindh Muller will be chairman.

MASSACHUSETTS GENERAL HOSPITAL

A research meeting will be held in the Bigelow Amphitheater of the Massachusetts General Hospital on Friday, May 6, at 4 p.m.

PROGRAM

- New Drugs in the Treatment of Parkinson's Disease
Dr. Robert Schwab
- The Pathologic Distribution of Water and Electrolytes in Patients after Duodenal Ulcer
Dr. Oliver Cope

BOSTON UNIVERSITY SCHOOL OF MEDICINE ALUMNI ASSOCIATION

The seventy-fifth annual reunion of Boston University School of Medicine Alumni Association will be held in the auditorium of the School of Medicine, 80 East Concord Street, Boston, on Friday, May 6.

The morning session, which will be held from 10 30 a.m. to 12 30 p.m., will be as follows:

- Some Problems Concerned with the Diagnosis and the Course of Prolonged Fever
Samuel Leard, M.D. (1942)
- Pharmacologic Approach to the Treatment of Neurogenic Disorders
Frederick F. Yonkman, M.D. (1939)
- Micelography — Indications and Significance
John D. Camp, M.D. (1922), assistant director, Section of Roentgenology, Mayo Clinic, Rochester, Minnesota
- Hormonal Alteration of Carcinoma of the Breast
Ira T. Nathanson, M.D.
- Seminoma of the Testicle Followed by Adenocarcinoma of the Breast
Presentation of case
Frank E. Barton, M.D. (1924)

Luncheon will be served at 1-00 p.m. in the main dining room, eighth floor, Evans Memorial Building, 65 East Newton Street (price, 75 cents). Luncheon tickets will be available at the School of Medicine Auditorium.

The afternoon session, which will be held from 2 to 4 p.m., will be as follows:

- Stump the Experts — Round-Table Discussion
Moderator, Samuel Vose, M.D.
- Chester S. Keefer, M.D. (Medicine)
- Reginald H. Smithwick, M.D. (Surgery)
- Leighton F. Johnson, M.D. (Otolaryngology)
- William Malamud, M.D. (Psychiatry)
- Joseph M. Foley, M.D. (Neurology)
- Donald G. Anderson, M.D. (Education, American Medical Association)
- Louis G. Howard, M.D. (Orthopedics)

Newer Antibiotic Agents, with Emphasis on Aureomycin and Chloromycetin William Hewitt, M D
Pharmacologic Tests and Diagnosis of Tumor of the Adrenal Gland Causing Paroxysmal Hypertension William E R Greer, M D (1943)

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater of Building D, Harvard Medical School, on Tuesday, May 10, at 8 00 p m The following program will be presented by the Department of Pharmacology, Harvard Medical School

Plasma Prostigmine Levels and Cholinesterase Inhibition in Dogs and Myasthenic Patients Avram Goldstein
Iodide Excretion in Dog and Man Douglas S Riggs and John B Stanbury
Effect of Cardiac Glycosides on Cardiac Tissue Metabolism Albert Wollenberger
Action of Pure Veratrum Alkaloids in Human Hypertension Edward Meilman and Otto Krayer
Antagonists to the Cardioaccelerator Action of Epinephrine Otto Krayer

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A meeting of the New England Society of Anesthesiologists will be held in the auditorium of Building A, Boston University School of Medicine, 80 East Concord Street, Boston, on Tuesday, May 10, at 8 p m The scientific program will be as follows

Heart Disease and Anesthesia Dr S Gilman
Subarachnoid Ephedrine Drs E Marchand and S Gilman
Some Observations on Anesthesia in Uremia Dr A Abrams

Physicians and medical students are invited

NORFOLK DISTRICT MEDICAL SOCIETY

The annual meeting of the Norfolk District Medical Society will be held at the Hotel Kenmore, Boston, on Wednesday, May 11

PROGRAM

5 15 p m Business meeting Embassy Room
6 00 p m President's Reception Social Hour
7 00 p m Annual Dinner Crystal Ball Room
Acceptance Speech W Richard Ohler, M D, incoming president
Greetings from the Massachusetts Medical Society Daniel B Reardon, M D, president
Remarks on Woman's Auxiliary Mrs James J Hepburn, president
Erwin D Canham, editor of the *Christian Science Monitor*, will speak on "The Role of the Press in the Present World Crisis"

SOUTH BOSTON MEDICAL SOCIETY

The annual dinner of the South Boston Medical Society will be held at the Harvard Club of Boston on Wednesday, May 11, at 6 30 p m The speaker will be Dr Norman Welch

HARVARD SCHOOL OF PUBLIC HEALTH

The Harvard School of Public Health announces that the Cutter Lecture on Preventive Medicine, initiated in 1917, will be held in Amphitheater D of the Harvard Medical School on Wednesday, May 11, 1949, at 5 p m Dr James C Spence, professor of child health, University of Durham, England, will speak on "Preventive Medicine The role of parents in child health" The medical profession, medical and public-health students and others interested are cordially invited to attend

MASSACHUSETTS SOCIETY OF EXAMINING PHYSICIANS

A meeting of the Massachusetts Society of Examining Physicians will be held at the Harvard Club, Boston, on Wednesday, May 11, at 7 p m Dr Donald Munro will speak on the subject "Total Rehabilitation of the Paraplegic Patient," with a film presentation

AMERICAN ORTHOPAEDIC ASSOCIATION

The sixty-second annual meeting of the American Orthopaedic Association will be held at the Broadmoor, Colorado Springs, Colorado, on May 18, 19, 20 and 21, under the presidency of Dr Ralph K Ghormley

The orthopedic surgeons of Denver, with Drs Robert G Packard and Atha Thomas as chairmen, have planned a clinical day in Denver on May 17 All members of the Association and their guests are invited Those planning to attend are requested to notify Dr Packard or Dr Thomas in advance, so that adequate arrangements may be made

SAMUEL D GROSS PRIZE

Essays will be received in competition for the Samuel D Gross Prize of \$1500 until January 1, 1950 The conditions annexed by the testator are the prize "shall be awarded every five years to the writer of the best original essay, not exceeding one hundred and fifty printed pages, octavo, in length, illustrative of some subject in Surgical Pathology or Surgical Practice founded upon original investigations, the candidates for the prize to be American citizens" It is expressly stipulated that the competitor who receives the prize shall publish his essay in book form, and that he shall deposit one copy of the work in the Samuel D Gross Library of the Philadelphia Academy of Surgery, and that on the title page it shall be stated that the essay was awarded the Samuel D Gross Prize of the Philadelphia Academy of Surgery

The essays, which must be written by a single author in the English language, should be sent to the Trustees of the Samuel D Gross Prize of the Philadelphia Academy of Surgery

(Notices concluded on page xiii)



For abrasions, cuts, wounds and such uses,
The ancients had herbs and their juices
Dr. Wise, in like need,
Just continues to read
The ads that he weekly peruses

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A DECADE'S EXPERIENCE IN THE OPERATION OF A GROUP MEDICAL-CARE ORGANIZATION*

SEYMOUR ETKIN, M.A.†

WASHINGTON, D. C.

THE National Health Assembly, which met last summer in Washington, D. C., reached agreement on everything except the question of national compulsory health insurance. Among the subjects agreed on was the proposal that voluntary prepayment was a sound method for financing health services.

Ten years ago such an agreement would have been impossible. At that time a storm raged within and without the medical profession over the question of prepaid health programs. The focal point of the storm was Group Health Association of Washington, D. C., a medical-care organization operating on the principles of group medical practice and the prepaid method of financing. Ten years ago programs of the type represented by Group Health Association were attacked as being forerunners of "socialized medicine." Today these programs are generally supported by all who are concerned with bringing medical care of the highest standard within the reach of all.

This article is a description and an analysis of the experience of Group Health Association from 1938 through 1947. In many respects the record is notable. Yet it is not without its shortcomings. No honest student of social welfare can afford to minimize them. It is my opinion that an honest appraisal of this experience will provide guidance to future changes in the organization of medical programs.

When the Association was organized in 1937, predictions concerning its future were of two kinds. One camp predicted that it would rapidly fold up and that its doctors would become outcast members of the medical profession. The other prophesied that this prepaid type of medical care would sweep the nation's capital because of its low-cost provisions and ensnare all the physicians in a monster octopus of regimentation and bureaucracy.

Actually, neither has happened. The Association is a respectable community organization attracting respectable residents of the Washington area to membership. Its physicians are accorded the same privileges in hospitals as other doctors in the District of Columbia and surrounding area. They have similar social status. They teach at the local universities. They are members in good standing in the District of Columbia Medical Society and the American Medical Association. Many of them have private practices, devoting only part of their time to Group Health Association member patients.

OPERATION OF MEDICAL SERVICE

The medical-service plan operates in this manner: members purchase a membership certificate and pay monthly dues. In return, with certain limitations and exceptions, members have a "blank check" on the medical services by Group Health. These services include diagnosis and treatment of ailments, major and minor surgical operations, use of facilities such as x-ray and laboratory procedures, and physical therapy. Members may avail themselves of physical checkups and other preventive care. Child care and obstetric service are provided. Eye examinations are given. Members may purchase lenses and frames through the Association at a reduced cost, and they may obtain prescriptions, drugs, vitamins and other pharmaceutical supplies at the pharmacies at a saving.

There are two types of membership: full service and nonhospitalization. Those who have full service pay larger monthly dues than those who have nonhospitalization memberships. Full-service members are eligible to receive hospitalization when necessary for sixty days in any calendar year, or in any one illness or condition, or continuous period of hospitalization. This includes a semiprivate room, general nursing, use of the operating or delivery room, services of the anesthetist, dressings and most medications, routine laboratory examinations, nursing care, emergency-room facilities and the use of an ambulance as requested by the attending physician.

*Nothing in this article is to be construed as an official pronouncement of the Bureau of the Census.

†Economist, Bureau of the Census, United States Department of Commerce; formerly member of administrative staff, Group Health Association.

A nonhospitalization member is entitled to all the services except the hospital services mentioned above

Changes in Benefits

Over the course of the Association's history, two divergent trends in the scope of benefits under its service program have appeared. One is toward more and more restrictions and limitations, and the other is toward greater liberalization of its program.

Restrictive trend When the first set of by-laws was adopted on March 22, 1937, there were relatively few restrictions on service. Only two impor-

The first set of by-laws restricted house calls within a radius of ten miles of the center of the District of Columbia. At the present time the radius is fifteen miles.

Other examples of liberalization of the service program are night clinics (tried for a time but discontinued), delivery service of pharmacy supplies, night telephone service, discount of 5 per cent for a year's prepayment of dues and 2 per cent for six months' prepayment, routine physical examinations encouraged, service to refugee children without cost, early infant-care classes and prenatal classes (not in operation at the present time), members drafted

TABLE 1 Partial List, Showing Development of Restrictions on Services Provided by Group Health Association

EFFECTIVE DATE	RESTRICTION	SOURCE
1937	Medical service not to include treatment of industrial accidents, operations on the brain or nervous system, mental cases, tuberculosis, drug or alcohol addiction.	Minutes, Board of Trustees, April 6, 1937
	Members to pay for the following items: medicines, drugs or surgical appliances, radium and deep x-ray treatments, oxygen tanks, tents or materials, blood transfusions.	
1938	\$1.00 charge for first house call in any illness. \$25.00 charge in maternity cases.	GHA News Letter, September 1938
June 1, 1939	Members to pay \$1.50 for x-ray film and material.	Minutes, Board of Trustees, May 24, 1939
August 1, 1939	Members with ailments or physical conditions requiring treatment, present at date of admission, to reimburse Association at cost for service rendered in connection with treatment.	Minutes, Board of Trustees, July 24, 1939
1939	During first 10 months of service, members to reimburse Association for cost of services including hospitalization connected with ailments present at admission, confinement and elective operations.	Minutes of Special Membership Meeting, November 21, 1939
September 3, 1940	Additional services not covered: plastic surgery, correction of deformities and birthmarks, psychiatric treatment and chiropody.	Minutes, Board of Trustees, September 9, 1940
August 1, 1941	Charge for obstetric care increased to \$50.00*.	Minutes, Board of Trustees, June 23, 1941
January 1, 1948	Those who have all services at cost except clinic consultations and routine laboratory services and all those 60 years of age or over admitted after January 1, 1948, are now restricted for all services — no exceptions — dues to apply against cost†.	Personal communication from Hospitalization Secretary, March 3, 1948

*At the present time this additional charge for obstetric care is \$100.00.
†Interestingly enough, the suggestion was made as early as 1939 that elderly dependents be required to pay for all services at cost (Minutes, Board of Trustees, September 18, 1939).

tant restrictions were embodied in the first set of by-laws. If a member became ill outside the Washington area, the Association reimbursed the member for expenses only up to the amount that would have been incurred had the member resided in the Washington area, and if a member's sickness was caused by a third person and the third person was required by law to pay for the member's sickness, the Association was entitled to reimbursement for the medical service furnished to the member.

As the Association developed, a gradual but ever-growing set of restrictions was adopted. Table 1 presents a partial list showing the development of these restrictions.

Liberalization trend On the other hand, there have been many examples of a liberalization in the service program. The first set of by-laws restricted membership to Government employees. In 1946 other employees became eligible to join on a group basis, and in 1947 they became eligible to join on an individual basis.

into military service could suspend membership, racial barriers dropped, and Negroes accepted for membership, health education forums (continued for a time but not in operation at the present time except for a series of psychiatric counseling forums on a fee basis), availability of optical service for the purchase of eyeglasses and frames at reduced cost, waiting period for service removed, and availability of child-guidance service.

MEMBERSHIP ELIGIBILITY

At the present time membership is open to all residents of the District of Columbia and vicinity. There are no restrictions concerning sex, race, occupation or place of employment. Up until January 1, 1948, there were no age restrictions, but on that date the restriction was imposed as noted in Table 1.

Participants may join on an individual basis or as part of a group.

Individual Enrollment

Individual applicants pay a \$2 00 application fee. This fee covers the expense involved in processing the application and in making laboratory tests such as urinalysis and blood tests.

Group Enrollment

No application fees are paid in a group enrollment. A group consists of employees of a single employer, or persons in one administrative unit of a business or Government agency or persons in one building or office. The percentage of those who must join to obtain group benefits varies according to the size of the basic unit.

Whether a person joins on an individual basis or with a group, a \$10 fee must be paid. This is the membership-certificate fee and gives the member voting and participating privileges in the organization. The \$10 membership fee covers all persons in a family unit unless more than one person desires to take out a membership certificate. The fee, which is the member's contribution toward the cost of the facilities and equipment purchased by the Association, is not refundable, but members who leave the Association may transfer their membership certificate under certain circumstances.

Through the membership certificate members have an equal share in ownership, and through an-

employees were permitted to join on a group basis. In February, 1947, any resident of the District of Columbia and vicinity was permitted to join on either a group or an individual basis.

By expansion of the promotion department and through an aggressive membership drive, large gains in membership were recorded in 1947. The most notable of these gains was due to the signing of contracts between Group Health Association and the Food and Agriculture Organization, the International Bank for Reconstruction and Development

TABLE 3 Rates of Accession and Secession in Membership, August, 1946, Through September, 1947

DATE	NO OF PARTICIPANTS AS OF END OF MONTH	NO OF ADMISSIONS	RATE OF ACCESSION	NO OF WITHDRAWALS	RATE OF SECESSION
			per 100 participants		per 100 participants
1946					
August	10 398	451	4.38	140	1.36
September	10 300	309	2.94	107	1.02
October	10 761	382	3.55	121	1.12
November	10 970	369	3.36	160	1.46
December	11 188	323	2.93	110	0.98
1947					
January	11 666*	270	2.31	158	1.42
February	12 073	474	3.93	67	0.55
March	12 216	213	1.74	70	0.62
April	12 177	235	1.93	274†	2.25
May	12 206	463	3.79	434†	3.56
June	12 346	394	3.19	254	2.02
July	12 679	435	3.35	302	2.38
August	12 806	360	2.81	233	1.82
September	13 522	974	7.20	256	1.91
Fourteen-month average			3.47		1.63

*This figure was adjusted by actual count of membership as a result of which 266 additional participants were picked up on the membership rolls.

†Withdrawals are concentrated owing to extensive cleaning out of pending withdrawals that had been hanging fire for six months or more.

TABLE 2 Membership Growth Group Health Association 1937-1947

YEAR	FIRST OF MONTH	NO OF MEMBERS	NO OF DEPENDENTS	TOTALS PARTICIPANTS
1937	Nov	900	*	*
1938	Nov	2 355	1 035	5 390
1939	Jan	2 115	2 759	4 874
1940	Jan	2 383	3 166	5 549
1941	Jan.	2 791	3 819	6 610
1942	Jan	3 284	4 309	7 793
1943	Jan	3 375	4 957	8 332
1944	Jan.	3 566	5 570	9 136
1945	Jan	3 253	5 427	8 680
1946	Jan	3 362	5 765	9 127
1947	Jan	4 097	7 457	11 554
1947	July	4 853	7 826	12 679

*Figures not available

nual elections of the board of trustees and votes on specific issues, as submitted to them, they determine the type and general character of its activities.

GROWTH IN MEMBERSHIP AND MEMBERSHIP TURNOVER

Table 2 shows the gradual rise in membership during the first ten years of operation. During the early years, the growth was fairly steady. During World War II, members were permitted to add dependents but new applications for membership were not accepted because of the difficulty in obtaining additional physicians and auxiliary medical personnel for the staff. When World War II ended, membership rolls were again opened and nongovernmental

and the International Monetary Fund. Under these agreements, the Association enrolled the employees of these agencies as group members.

Increase in membership through admission of new applicants has been retarded by the withdrawal of members who resign or suspend the membership of a dependent for one reason or another. For instance, during the fourteen months from August, 1946, to September, 1947, for every 7 new participants added, about 3 old participants withdrew. (The actual figures are 3.47 new participants as against 1.63 withdrawn participants and are derived from Table 3.) According to Miss Dorothy Sharrow, administrative assistant to the executive director, about 90 per cent of those who withdraw give as reasons the fact that they are moving away from the city. However, the extent to which other factors have caused members to withdraw or suspend membership is analyzed below.

MEMBERSHIP CHARACTERISTICS

Family Status

By types of family unit, the largest proportion of memberships consisted of member, spouse and one or more children (Table 4).

A comprehensive survey made in 1942 showed that at that time approximately a third of the participants were in the "member only" category, another third comprising the "member and spouse only" group.²

In 1947 the average number of participants in each membership was 2.6.¹ In 1942 it had been 2.3.²

Though the average size of family unit has increased from 1942 to 1947, the families* are small, compared to those in an urban population.

Other important features of the 1942 survey showed that participants, compared to an urban

TABLE 4 *Distribution by Types of Family Unit, March, 1947**

TYPE OF MEMBERSHIP	PERCENTAGE
Member spouse and children	45.7
Member only	27.1
Member and spouse only	19.5
Other (all types of family units, including adult dependents)	7.7

*Based on Number and Composition of Group Health Membership.¹

population group, consist of a larger proportion who are married and a smaller proportion widowed or divorced.²

Age of Participant

A sample study of the ages of members was made in 1947 by examination of the entrance age of every fifth member participant who joined between May, 1944, and July, 1946. The ages at time of entrance are presented in Table 5, which shows that over

TABLE 5 *Entrance Age of Sample Group*

AGE	NO OF MEMBERS	PERCENTAGE OF TOTAL
57		
Newborn infants	27	6
0-4 years	66	14
5-20 years	59	12
21-44 years	289	61
45-59 years	29	6
60 and over	4	1
Total	474	

90 per cent of new member participants were under 45 years of age at the time of the study.

The more comprehensive study made in 1942 showed, by actual count, that half the members were between 20 and 34 years of age and only an eighth 50 years old or over. The median age for all participants was 29.7 years, the median age for male participants being 30.1 and that for female participants 29.3.²

*All members of a family are not always included as a member's dependent for service, but it is my impression that the number of dependents who are not listed is very small.

DUES AND FEES

The cost of monthly dues depends on the type of membership and the size of the member's family. The present rates are shown in Table 6.

Limitations and Exceptions Under Dues System

Obstetric care. When obtaining prenatal, delivery and post-partum care, the member pays the first \$100 toward the hospital bill when both parents have been listed for membership for ten months prior to expected delivery. When obstetric service is obtained in cases in which delivery is expected before ten months of continuous membership, the member meets the entire hospital bill and pays to the Association an additional \$75.00.

Cost of Materials

The expenses of materials, such as x-ray films, serums, eyeglasses and lenses, are paid by members. These are usually purchased from the Association's pharmacies or Optical Department. There are special charges for electrocardiograph materials, basal-metabolic-test materials, x-ray therapy, phys-

TABLE 6 *Cost of Dues*

PARTICIPANT	MONTHLY DUES	
	WITH HOSPITALIZATION	WITHOUT HOSPITALIZATION
Member	\$3.50	\$3.00
Adult dependent	3.50	3.00
Child dependent (for each of first three children — no charge for more than three children)	2.25	2.00

ical therapy and laboratory test materials. Some of these material charges appear to be actually service charges—for example, x-ray and physical therapy. A charge of \$1.00 is placed on each x-ray and physical-therapy treatment rendered, "to compensate for heavy wear on expensive equipment," according to the *Minutes* of the Board of Trustees (July 8, 1947). If these are actually service charges the principle of removing barriers to medical care is being violated because service charges are apt to constitute "hesitation fees"—that is, fees that cause participants to neglect medical attention because of additional costs involved.

Restricted services. On the basis of laboratory tests, medical histories and physical examinations, certain types of medical conditions existing prior to membership are determined. Members who join on an individual basis (nongroup) may be restricted for services under the monthly dues for specific conditions present at time of admission. Service for these restricted conditions is given on a cost basis.

Limitations of Service

There is some evidence that the present rates of dues and other fees are so high that the Associa-

tion is attracting only people with the highest family incomes

In 1939 the median salary of members was \$2700, and 53 per cent of the members had salaries under \$3000 per year. A survey for 1946 indicated that the median family income was about \$5600.

The original purpose of GHA was to provide the best type of medical care to those who usually could not afford it. What is needed is a comprehensive study to determine whether the program has become "selective" in its operation.

QUALITY OF MEDICAL SERVICE

In his report at the annual membership meeting in February, 1947, former president Harry J. Becker stated:

We have nearly completed the recruitment for the medical care organization which a year ago was largely a dream on paper. We are happy to report that we have been able to recruit professional staff to meet substantially the medical care requirements for our membership. For the first time in a long while we have as many general physicians as are necessary to maintain our medical standards. Medical judgment will support my statement that the members of Group Health are today enjoying a better quality of medical care than can be purchased on either a prepaid or fee-for-service basis elsewhere in Washington. We have available to any member of the Washington community the most completely equipped and staffed out-patient service in Washington utilizing the principle of the group practice of medicine.

It is beyond the scope of this article to pass medical judgment on the caliber of the Association's medical staff. However, one method of appraising the quality of the medical care program is by considering member reaction to the program.

A survey made in the summer of 1947 indicated that the three aspects of the program most appreciated by the members were the competence of the medical staff, the prepayment features of paying for medical care, which afforded insurance against large medical bills, and the scope of service available.

However, member reaction to the program has often been negative. A study of the records of separation for four selected months (Table 7) indicated that from 4 to 20 per cent of those who are separated in any one month are separated because of dissatisfaction with the service. It is also possible that there are among those who give no reason for requesting separation members who are dissatisfied with the service but who prefer not to state their reasons. (On the other hand, the administrative assistant to the executive director has stated that 90 per cent of current separations are due to the fact that participants are leaving the Washington metropolitan area.)

Unsatisfactory service does not always lead to the stage where the member requests separation. For the ten months from June, 1946, through March, 1947, the Complaints and Suggestions Committee

received 54 complaint letters and 16 letters suggesting ways of improving the service.

Complaints and suggestions are usually received by the Association in writing to assure accurate transmittal of the members' view.* They are routed to the executive director, who consults interested parties, gets other information as needed and takes such action as he considers to be the best interests of the Association. The Complaints and Suggestions Committee at its monthly meetings reviews the papers, searching for factors that may have been overlooked. The purpose is to determine the essen-

TABLE 7 Separations by Suspension or Resignation for Selected Months

REASON	NO OF PARTICIPANTS	PERCENTAGE OF TOTAL SEPARATIONS
April 1946		
Leaving area	40	50
Receiving medical care elsewhere	10	9
Dues increase	4	5
Dissatisfied with service	21	20
Not given	51	29
Total	106	
December 1947		
Leaving area	72	46
Receiving medical care elsewhere	1	1
Dissatisfied with service	6	4
Not given	18	11
Other (deceased, membership transferred to dependent and so forth)	61	38
Total	158	
January 1948		
Leaving area	100	63
Receiving medical care elsewhere	5	3
Dissatisfied with service	6	4
Not given	31	19
Other	18	11
Total	160	
February 1948		
Leaving area	64	45
Receiving medical care elsewhere	6	4
Dissatisfied with service	6	4
Not given	60	41
Other	11	8
Total	147	

tial nature of the complaint and find underlying causes.

Many items of criticism and suggestions for improving the service were received in a recent survey. Most of all, members wanted the Association to expand its services to include dental care, a psychiatric program and other medical facilities not now provided on a prepaid basis. The two greatest limitations on the program, according to member opinion, are its telephone service and its appointment scheduling.

A survey made in 1942² revealed the following:

The turnover of membership which occurred prior to 1942 affected primarily the younger group. The older members showed a greater degree of stability. Almost two thirds [of the participants] who were 50 years old or over on January 1, 1942 joined the organization before

*Obviously not all complaints are reduced to writing and many complaints never reach the organization.

January 1, 1939, whereas only 38% of the present membership as a whole joined before that date. Less than 5% of the members who joined in 1941 were 50 years old or over, but 20% of the present membership who joined before 1939 are in that age group now.

INFANT AND MATERNAL MORTALITY AND GENERAL DEATH RATES

Infant Death Rate

A reliable barometer of the health of any segment of the population is the infant mortality rate of

From Table 8 it will be seen that for every year for which data have been recorded (only data missing are those from November 1, 1937, the date of initial operation of the Group Health Association, to December 31, 1938), the Association's infant mortality rate is lower than that for the white population of the District of Columbia.

Taken by themselves, the infant mortality rates appear remarkably low. From 1939 to 1946, the average was 14.2 deaths per thousand live births per year (standard error of deviation 2.734) as compared with an average of 32.9 infant deaths per thousand live births for the white population of the District of Columbia during the same period. It would be still more remarkable, however, if the results were less striking in view of the fact that the family incomes of members are probably higher than those of the "average" white family in the District of Columbia.

Adequate incomes make possible healthful living, provide proper diets for expectant mothers and per-

TABLE 8 Infant Mortality, Group Health Association and White Population of the District of Columbia, 1937-1946 *

YEAR	GROUP HEALTH ASSOCIATION			DISTRICT OF COLUMBIA WHITE POPULATION	
	NO. OF LIVE BIRTHS	NO. OF INFANT DEATHS	RATE PER THOUSAND LIVE BIRTHS	RATE PER THOUSAND LIVE BIRTHS	
1937†	—	—	—	—	
1938†	—	—	—	—	
1939	109	1	9.1	33.6	
1940	151	4	26.0	36.8	
1941	233	4	17.0	38.7	
1942	281	6	21.0	39.2	
1943	309	3	8.2	28.5	
1944	323	6	18.6	27.7	
1945	256	0	0	29.6	
1946	345	5	14.0	29.5	
Totals	2,007	29			
Averages			14.2†	32.9	

*Figures for Group Health Association supplied by Statistical Department Group Health Association and figures for the District of Columbia by Health Department District of Columbia.

†No data available for Group Health Association.

‡The standard error of this arithmetic mean is 2.734. "Knowledge of this standard deviation or standard error" says Mills "enables us to set limits within which it is highly likely that the true mean lies."

TABLE 9 Maternal Deaths for White Population of District of Columbia, 1937-1946

YEAR	RATE PER THOUSAND LIVE BIRTHS
1937	3.6
1938	4.2
1939	3.7
1940	2.4
1941	2.3
1942	1.7
1943	1.3
1944	0.8
1945	0.2
1946	0.5

the group. This index is the number of infant deaths per thousand live births. An infant death is a death occurring when the child is less than one year of age and does not include stillbirths.

According to Sir Arthur Newsholme, an outstanding British authority on public health, "Infant mortality is the most sensitive index we possess of social welfare. If babies were well-born and well-cared for, their mortality would be negligible."

Dr. George C. Ruhland, health officer for the District of Columbia, terms infant mortality "the most delicate indicator of the health mindedness of a community and the nation."

Data on infant mortality for babies born to members are available and are reproduced in Table 8, compared to the infant mortality rates for the white population in the District of Columbia.

Since the composition of the Association is almost entirely white, it was believed that a more valid comparison would result by the use of infant mortality figures for the white population in the District of Columbia rather than the general (Negro and white) average.*

*It is generally agreed that there is a great disparity in the relative health level of Negroes and whites. The life expectancy of Negroes is approximately ten to twelve years shorter than that of whites; approximately three times as many Negro males and four times as many females proportionately die of tuberculosis. The death rate from heart disease is also considerably greater among Negroes than among whites.

mit needed rest for pregnant women. The relation between economic factors and health has often been stated but rarely more effectively than in a recent radio broadcast.

What is health? It's not the great operation. It's not the surgeon and his sterile rubber gloves. It's not a test tube full of vitamins. Vitamins, yes. But not in test tubes. In people. Health is day to day living, the food you eat, the clothes you wear, the house you live in. The size of the town in which you're born. The kind of water supply and sewage disposal. Is the road to your house good enough so the doctor can get there on a rainy day? Health is the number of dollars a week your father earns. Health is the teacher in the fourth grade who sees you squinting and tells your mother. Health is love and understanding when you're an infant. All these things. Many more. You can't solve it with a quick dramatic operation.

I do not wish to belittle the competence of the Association's obstetric staff or the adequacy of the prenatal, delivery and postnatal care given to members. However, since members use the same hospital facilities as other white persons in the community, and since Group Health Association obstetricians and pediatricians are not supermen, the remarkable difference between infant mortality rates shown in Table 8 can be partially ascribed to

the suspected high family income levels of members mentioned above and the fact that, with very few exceptions, births occurred in the hospitals rather than in homes

This last factor was a greater influence in explaining the difference in infant mortality rates in the early years of operation from those in recent years. The proportion of hospital deliveries of white mothers in the District of Columbia has been steadily increasing during the past decade. In 1937, 95.1 per cent of births for the white population occurred in hospitals, in 1946, 99 per cent of these births occurred in hospitals.

Maternal Death Rates

The maternal death rate is another index of general health effectiveness in a community.

About 2000 babies have been born to Group Health Association mothers in the last ten years without a maternal death. For the white population in the District of Columbia, maternal death rates per thousand live births are shown in Table 9.

General Mortality Rates

Table 10 shows the general mortality rates for Group Health Association members from 1938 to

TABLE 10 *Mortality for Group Health Association Members, 1938-1946*

YEAR	TOTAL NO OF PARTICIPANTS AS OF JANUARY 1	AVERAGE NO OF PARTICIPANTS FOR YEAR*	NO OF DEATHS	RATE PER THOUSAND PARTICIPANTS
1938	—	—	5 ^(†)	—
1939	4,874	5,211	24	4.61
1940	5,549	6,079	15	2.47
1941	6,610	7,210	17	2.36
1942	7,793	8,062	22	2.75
1943	8,332	8,734	22	2.52
1944	9,136	8,908	30	3.37
1945	8,680	8,905	19	2.14
1946	9,127	10,046	23	2.29
1939-1946	—	62,150	172†	2.72

*Computed by use of two-year moving averages with exception of figure for year 1946. In 1946 the number of members is an average of the membership levels at the end of each month of that year.

†Five (5) deaths in 1938 omitted from total.

1946. For purposes of comparison the mortality rates for the District of Columbia for all causes, all colors, and those for all causes in the white population are listed in Table 11. It will be seen that the death rates among Association participants are lower than those for the District of Columbia for

every year for which statistics of Group Health Association mortality are available.

As shown in Table 10, the average mortality rate for the years 1939-1946 for Group Health Association members is 2.72 per thousand population. However, when specific death rates* are applied to the composition of the membership for 1942 (the only year for which the composition of membership by sex and age is available), it is found that the expected death rate is 6.57.

In other words, part of the low death rate is explained by the fact that, on the basis of the com-

TABLE 11 *Mortality Rates of Group Health Association Members Compared with Those for Others in the District of Columbia, 1939-1946*

YEAR	GROUP HEALTH ASSOCIATION RATE	DISTRICT OF COLUMBIA RATE*	
		ALL CAUSES ALL RACES	ALL CAUSES WHITE RACE
1939	4.6	13.0	11.2
1940	2.5	13.5	12.1
1941	2.3	11.8	10.5
1942	2.7	11.1	9.4
1943	2.5	10.9	9.8
1944	3.4	10.0	8.6
1945	2.1	10.4	8.7

*Source: Department of Health, Washington, D. C.

position of its participants as of January 1, 1942, its members are relatively young, women preponderate, and the participants are predominantly white.

However, in view of the extraordinarily low death rate over a period of years, it may be concluded that factors other than age, sex and race are responsible. What these factors are and to what extent they influenced the mortality rate are not definitely known. It can only be surmised that these factors include the relatively high socioeconomic levels of participating families and the arrangement under which members obtain their medical care.

*A specific death rate is one for a selected population group usually based on race, sex and age.

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2. Interim report of the Subcommittee on Statistics, Records and Research. *Minute Record Book*. 3 pp. (mimeographed). May 1, 1942.
3. Mills, F. C. *Statistical Methods Applied to economics and business*. 746 pp. New York: Henry Holt & Co. 1935. P. 466.
4. *A Long Life and a Merry One*. Radio program. Columbia Broadcasting System, April 4, 1947.

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ciated with leg pains, a heart murmur was noted, and his pulse was said to have been unusually slow, but no exact details were obtainable. Through school and college he led a very active life. He was an ardent tennis player and participated in all types of sports.

In 1939 the patient was rejected for the Navy because of an elevated blood pressure. Consequently he was examined at the Massachusetts General Hospital Out-Patient Department (U No 223487). Examination at that time showed a regular cardiac rate at 70, systolic and diastolic murmurs at the base and apex of the heart, and a blood pressure of 180/65 in both arms whereas in the legs the systolic pressure was 140. Diagnosis was deferred, and the patient was sent for chest x-ray films, which were reported as showing hypertrophy of the left ventricle without evident rib changes (November 15, 1939). The patient never returned for follow-up examination.

In 1943, when he again attempted to enlist in the Navy, he was told that his blood pressure was 230/80 and that he had coarctation of the aorta. He remained entirely asymptomatic and led an active life until May, 1946. At that time, while working under considerable pressure, he first experienced a blackout, during which he had a mild generalized convulsion and became unconscious for about a minute. This type of episode was repeated on frequent occasions in subsequent years. An electroencephalogram taken on suspicion of epilepsy was stated to have been normal.

In July an electrocardiogram was reported as showing complete heart block, and it was believed that the seizures were of the Adams-Stokes type. Treatment with ephedrine and atropine was followed by a temporary decrease in the number of attacks.

In August, because of blackouts increasing in frequency, up to several an hour, as well as "brownouts," consisting of weakness and faintness without convulsive movements or loss of consciousness, the patient was referred to us*. He denied joint pains, symptoms of infection, dyspnea, chest pain or any other symptomatology.

The family history indicated that his father and mother were both living and well, two siblings were in excellent health. He had been married for 5 years and had a 2-year-old child, his wife and child were well.

Physical examination revealed a thin but fairly well developed man appearing tense and concerned over his condition but not acutely ill. The neck vessels showed a vigorous collapsing type of arterial pulsations but no abnormal venous fullness. The cardiac apical beat was forceful and felt in the fifth interspace 1 cm. outside the midclavicular line. There was a harsh Grade II to III systolic murmur at the base, heard loudest in the second left interspace, but radiating all over the precordium, especially toward the lower sternal areas. The murmur radiated into the neck vessels and was heard loudly over the upper dorsal spine. Also at the base there was a high-pitched, Grade II, blowing diastolic murmur heard equally to the right and left of the sternum in the second interspaces and radiating down the sternal borders. The aortic second sound was greater than the pulmonary second sound. The first sound at the apex was forceful but variable in intensity, and a Grade II systolic murmur was heard in this area, together with a rather loud third sound. No thrill was made out. Definite intercostal pulsations were felt in the posterior axillary line. The lungs were clear and resonant. The abdomen was not remarkable. The liver and spleen were not felt. The femoral and dorsalis pedis pulsations were palpable but definitely reduced.

The pulse rate at the time of examination was 48 and somewhat irregular. The temperature was normal. The blood pressure in both arms was 200/60. The systolic blood pressure in the legs was 100, and the diastolic was questionable at 70.

During the examination the patient had no blackouts. An electrocardiogram made at the time showed varying degrees of heart block ranging from complete dissociation to simple first-degree block with a varying PR prolongation. The basic pattern was the same as that shown in Figure 1.

The patient was admitted to the Winchester Hospital for further observation and treatment. Routine blood and urine studies were not remarkable. A blood Hinton test was negative. Three blood cultures were negative. Electrocardiograms on various occasions showed normal sinus

rhythm at a rate of 90 with a PR interval of 0.22 second as demonstrated in Figure 1A, and again, complete auriculoventricular dissociation with a ventricular rate of 45, as in Figure 1B. Unfortunately, no tracing was obtained during an attack. X-ray studies of the heart showed prominence of the left ventricle, with unusually vigorous contractions. The aortic knob was small. The left auricle was not remarkable. The transverse diameter of the heart measured 13.9 cm., as compared with an internal chest diameter of 28.2 cm. The lung fields were normal. There was slight but

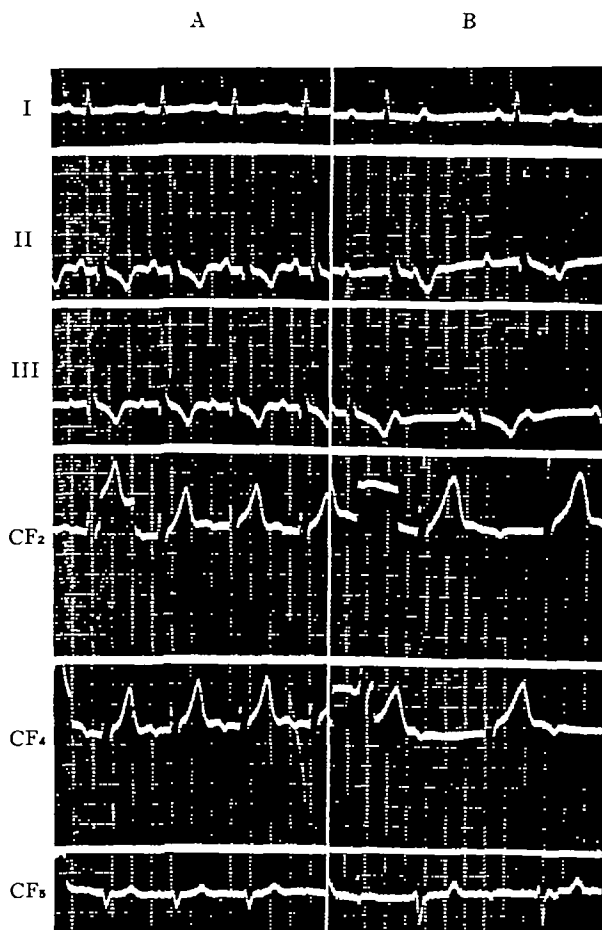


FIGURE 1 Electrocardiograms in a Case of Coarctation of the Aorta

A shows regular sinus rhythm at a rate of 90, with a PR interval of 0.22 second, the T waves are low and upright in Lead I, inverted in Leads 2 and 3, with sagging ST segments and 1.5-mm Q waves and prominent T waves in Leads CF₂ and CF₄, with relatively low R and deep S waves. The R wave is very low in Lead CF₂, with upright T waves. B shows complete auriculoventricular dissociation, with a ventricular rate of 45 and an auricular rate of 90.

definite notching of the ribs. The temperature remained normal. The blood pressure in the arms varied from 190/50 to 210/60. Two milligrams of epinephrine in oil was given intramuscularly twice daily, and 0.65 mg. of atropine by mouth thrice daily. There was continued shifting in the heart rate from about 90 to about 40, several times daily. At intervals the patient had mild "brownouts," but none of the blackouts.

After a week of hospitalization he was discharged on ephedrine sulfate, 48 mg. three times daily, and atropine sulfate, 0.65 mg. four times daily by mouth. The first week at home he had two mild blackouts, but subsequent to this he had

*We are indebted to Dr. J. M. Wilcox of Woburn, Massachusetts, who referred the patient and kindly consented to his being followed thereafter.

COARCTATION OF THE AORTA ASSOCIATED WITH ADAMS-STOKES SYNDROME, COMPLETE HEART BLOCK AND BICUSPID CALCAREOUS AORTIC VALVE

Report of a Case

RICHARD J. CLARK, M.D.,* AND HARLAN I. FIRMINGER, M.D.†

WINCHESTER, MASSACHUSETTS, AND BETHESDA, MARYLAND

TO OUR knowledge coarctation of the aorta in association with complete heart block and Adams-Stokes syndrome has not previously been reported. The patient in the case reported below was first observed while having attacks of Adams-Stokes syndrome. Examination revealed signs characteristic of coarctation of the aorta. Varying degrees of heart block were manifest and subsequently became complete. Post-mortem examination showed, in addition to coarctation, a calcified bicuspid aortic valve. The cause of the heart block prompted considerable debate prior to death.

REVIEW OF THE LITERATURE

Coarctation of the aorta has been very thoroughly discussed in its clinical and pathological aspects. Virtually all autopsied cases in the literature were assembled by Abbott¹ up to 1928, and subsequent cases over two years of age up to 1946 by Reifenstein, Levine and Gross.² From these reviews it may be observed that bicuspid aortic valves are of such frequent occurrence as to be almost considered a part of the coarctation syndrome, in the first report they were found in 25 per cent of 183 cases¹, in the second this anomaly was present in 42 per cent of 104 cases.² It is emphasized that these bicuspid valves are a vulnerable focus for subacute bacterial endocarditis and other types of valvulitis. Among the patients living to adult age, the development of a calcareous aortic valve is not unusual, Reifenstein et al.² described 11 cases of "calcific aortic stenosis" among 93 patients, in which fairly complete valvular descriptions were available.

The subject of complete heart block in younger age groups has recently been discussed by Crawford and Di Gregorio,³ who itemize various possible causes and review the literature of complete heart block due to congenital heart disease. The following criteria have been set up for congenital heart block: proof by graphic methods, knowledge of a slow pulse at an early age, signs of congenital heart disease, and absence of a history of infection or other factors that might produce heart block. Fifty cases have been reported in which complete heart block has appeared to be of congenital origin. Yater et al.^{4, 5} have reviewed and reported the greater number of these. The associated congenital lesions have included ventricular septal defects as the most

common (26 out of 44 cases),⁴ patent ductus arteriosus, auricular septal defects, pulmonary stenosis, transposition of the great vessels, common aorta and pulmonary artery, and cor triatriatum.

Waldman⁶ reported a case of patent ductus arteriosus with transient heart block and mild Adams-Stokes attacks. This was the first such case of congenital heart disease in which a cardiogram was obtained during an attack. Faessler⁷ reported 8 cases of Adams-Stokes syndrome with congenital heart disease, 6 patients having complete block between attacks, of these, 6 cases were diagnosed as ventricular septal defects, 1 as a patent ductus, and 1 as a persistent foramen ovale. Waldman⁶ points out that heart block in congenital heart disease may be present as a part of the congenital defect or may be acquired and superimposed upon the congenital deformity. Prior to post-mortem examination it might have been argued that the case reported below could fit into the former category, but subsequently the latter explanation appeared probable.

Complete heart block in calcareous aortic stenosis has recently been reviewed by Warshawsky and Abramson.⁸ They report a case in a fifty-two-year-old patient with rheumatic heart disease manifested by aortic stenosis and insufficiency, showing calcific extension from the aortic valve into the membranous portion of the interventricular septum. Dry and Willius,⁹ in a study of calcareous aortic stenosis, found 1 case, out of 63 examined post mortem, that showed complete heart block with a nodular excrescence of calcium extending from the mitral cusp of the aortic valve in such a manner as to involve the bundle of His. In their series of 85 cases with marked clinical evidence of calcareous aortic stenosis, 2 showed complete heart block, and 5 others, delayed auriculoventricular conduction. In a study of 22 cases of calcific aortic stenosis, Reich¹⁰ found 1 case of rheumatic etiology that showed complete heart block and left-bundle-branch block. Boas¹¹ reported 2 out of 6 cases of aortic stenosis that showed complete heart block. Cohen et al.,¹² in an analysis of 9 cases of calcareous aortic stenosis, described 1 with complete heart block.

CASE REPORT

L. A. M., a 31-year-old married schoolteacher was first seen by one of us (R. J. C.) in August, 1946. He was considered to have been normal at the time of birth. He had had a vague illness at the age of 10 for about 10 days, asso-

*Assistant physician Massachusetts General Hospital; assistant cardiologist Boston Lying-in Hospital; cardiologist, Winchester Hospital.

†Pathologist, National Institute of Health, United States Public Health Service; formerly resident pathologist, Massachusetts General Hospital.

The lung sections showed small, patchy areas of atelectasis, and the alveolar walls appeared slightly thickened. Frequent areas of large confluent alveoli containing septal remnants with bulbous tips were present.

There was moderate sclerosis of the small arteries within the substance of the brain, especially in the gray matter. In the white matter, in addition, there were scattered phagocytes containing brown hemosiderin pigment in the perivascular spaces of some of these vessels.

The pathological diagnoses were coarctation of the aorta, bicuspid aortic valve, calcific aortic valve with stenosis and insufficiency, cardiac hypertrophy and dilatation, auriculo-ventricular block, complete, clinical, interstitial fibrosis of the myocardium in the region of the bundle of His, fibrous pericardial adhesion, acute passive congestion of the liver, spleen and intestines, peripheral edema of the lower extremities, and pulmonary emphysema.

DISCUSSION

There was little doubt from the first that this patient suffered primarily from coarctation of the aorta and heart block. The chief problem was the interpretation of the murmurs and the explanation of the cause of the heart block.

In the present day of surgical correction for coarctation, the interpretation of murmurs becomes increasingly important as an indication of possible complicating lesions. The classic murmur of coarctation is described as a basal systolic murmur of slight to moderate intensity, with radiation to the upper dorsal spine. However, numerous variations have been reported, from complete absence of murmurs to a systolic murmur heard only posteriorly. The presence of associated diastolic murmurs at the base has been mentioned in various articles. Reifenstein et al.² stated that diastolic murmurs were present in 20 of their 104 cases, in each of which, where the valves were described, there was either aortic-valve disease or a patent ductus arteriosus. In a clinical series of 40 cases of coarctation observed by one of us (R. J. C.),¹⁴ basal diastolic murmurs were heard in 14, and an additional 5 showed this finding on phonocardiography, giving a total of 47 per cent. Reifenstein and his associates² found bicuspid aortic valves in 42 per cent of their series. It has been suggested that in the presence of coarctation with high pressure in the proximal aorta, bicuspid aortic valves may give rise to a diastolic murmur. Although this relation has not been proved, the correlations are suggestive. Rheumatic valvular disease in association with coarctation is not unusual, being present in 20 1/4 per cent of the series reported by Reifenstein et al.² Apical murmurs may be secondary to the coarctation or due to separate mitral-valve disease.

In the case under discussion there was a suggestive history of rheumatic fever at the age of ten. We first considered that accompanying rheumatic aortic valvulitis might account for the basal diastolic murmur, but because of the frequency of associated bicuspid aortic valves this diagnosis was also postulated. The basal systolic murmur was considered as arising from the coarctation. The murmur radiated into the neck, which is not uncommon in this

condition. The aortic second sound was present and no thrill was made out. For these reasons a clinical diagnosis of aortic stenosis was not made.

Because of the heart block and the moderately loud systolic murmur along the sternum, the possibility of an accompanying ventricular septal defect was strongly entertained. This case and others in the literature suggest that the diagnosis may be made too often because of the presence of heart block.

The basic electrocardiographic pattern with the inverted T waves and small Q waves in Leads 2 and 3, as well as the high T waves in the chest leads, raised the question of coronary-artery disease, either congenital or acquired, as a factor in the heart block. There was no suggestion of coronary-artery pain, the T waves were not typical of coronary thrombosis, and patterns over a period of observation showed no significant change. It was thought more likely, and confirmed subsequently at autopsy, that this tracing represented left ventricular strain in a vertically placed heart.*

The degree of hypertension that developed in the last six to eight months of life is unusual in coarctation and probably in part a factor of compensation for the complete heart block. This appeared in spite of marked aortic stenosis. It is interesting that the patient complained of none of the symptoms usually referable to hypertension, possibly because of the low diastolic level associated with aortic insufficiency.

Treatment of this case was symptomatic and general. Surgical plastic repair was briefly considered, but it was thought that the obvious complications, together with the patient's age, were absolute contraindications. Sympathectomy was also discussed but dismissed, again because of the patient's condition and because of relatively unfavorable results in other less complicated cases.¹⁴ This case demonstrated the value of epinephrine in acute phases of Adams-Stokes syndrome and the fact that such acute phases usually subside over a period of time with the clearing of block or establishment of fixed complete block.

The post-mortem examination although explaining much of the clinical picture, also provided other problems, one was the explanation of the unusual aortic valve. Lewis and Grant,¹³ in their study of congenital bicuspid aortic valves, found that the annulus fibrosus failed to break through the aortic media normally. Koletsky,¹⁵ in a study of 18 cases described two types, in one group there was a simple bicuspid valve, and in the other there was a rudimentary congenital ridge showing some attempt to form three cusps. The case under discussion seemed to fit into the latter class. The only questionable point was the superficial position of the annulus

*It is of interest that we have recently observed 2 other cases in young men at the Massachusetts General Hospital with coarctation showing almost the identical pattern.

The lung sections showed small, patchy areas of atelectasis, and the alveolar walls appeared slightly thickened. Frequent areas of large confluent alveoli containing septal remnants with bulbous tips were present.

There was moderate sclerosis of the small arteries within the substance of the brain, especially in the gray matter. In the white matter, in addition, there were scattered phagocytes containing brown hemosiderin pigment in the perivascular spaces of some of these vessels.

The pathological diagnoses were coarctation of the aorta, bicuspid aortic valve, calcific aortic valve with stenosis and insufficiency, cardiac hypertrophy and dilatation, auriculo-ventricular block, complete, clinical, interstitial fibrosis of the myocardium in the region of the bundle of His, fibrous pericardial adhesion, acute passive congestion of the liver, spleen and intestines, peripheral edema of the lower extremities, and pulmonary emphysema.

DISCUSSION

There was little doubt from the first that this patient suffered primarily from coarctation of the aorta and heart block. The chief problem was the interpretation of the murmurs and the explanation of the cause of the heart block.

In the present day of surgical correction for coarctation, the interpretation of murmurs becomes increasingly important as an indication of possible complicating lesions. The classic murmur of coarctation is described as a basal systolic murmur of slight to moderate intensity, with radiation to the upper dorsal spine. However, numerous variations have been reported, from complete absence of murmurs to a systolic murmur heard only posteriorly. The presence of associated diastolic murmurs at the base has been mentioned in various articles. Reifenstein et al.² stated that diastolic murmurs were present in 20 of their 104 cases, in each of which, where the valves were described, there was either aortic-valve disease or a patent ductus arteriosus. In a clinical series of 40 cases of coarctation observed by one of us (R. J. C.),¹⁴ basal diastolic murmurs were heard in 14, and an additional 5 showed this finding on phonocardiography, giving a total of 47 per cent. Reifenstein and his associates² found bicuspid aortic valves in 42 per cent of their series. It has been suggested that in the presence of coarctation with high pressure in the proximal aorta, bicuspid aortic valves may give rise to a diastolic murmur. Although this relation has not been proved, the correlations are suggestive. Rheumatic valvular disease in association with coarctation is not unusual, being present in 20 1/2 per cent of the series reported by Reifenstein et al.² Apical murmurs may be secondary to the coarctation or due to separate mitral-valve disease.

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only "brownouts" occurring with shifts in pulse rate from 80 to 40, which occurred off and on once or twice daily. In September he resumed teaching. In late October his heart was remaining in complete block most of the time. By mid-November his rhythm settled into permanent block at a rate of 40, and he was quite symptom free. During the winter, spring and summer he led an active life, often walking 5 miles a day. His blood pressure in the arms gradually increased up to 290/50. The heart size increased 4 cm in the transverse diameter. Complete heart block with a ventricular rate of 40 persisted. Apart from some increase in nervous irritability he felt well.

On November 16, 1947, the patient got up feeling as usual. He had flown to New York City on the previous day to attend a football game. In midmorning he remarked that

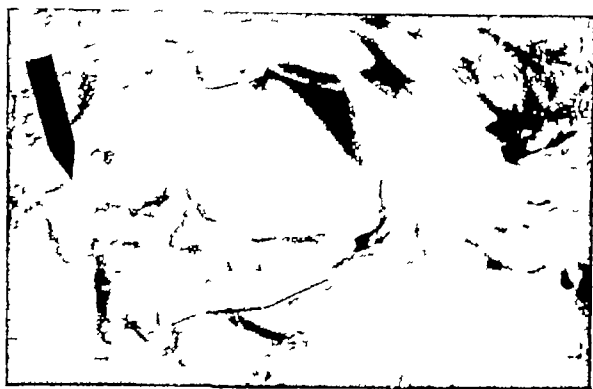


FIGURE 2 Gross Specimen of the Aortic Valve

The arrow indicates the rudimentary ridge between two coronary cusps, the right coronary cusp is on the left, and most of the leaf is on the right of the plate. (Note L-shaped calcific mass below)

his heart felt as though it were "going to be jumpy," and he took a dose of atropine. He seemed nervously irritable. On returning from church he sat down to read the paper. He suddenly put the paper down and stated that he felt smothered, his eyes rolled upward, and he took several short gasps, became pallid and apparently expired within 2 or 3 minutes.

Post-mortem examination revealed a well developed man, 5 feet, 7 inches, in height and weighing about 150 pounds. He appeared at least 5 years younger than his actual age of 32. Slight edema was evident in the lower legs and ankles.

Examination of the thoracic organs showed light and doughy lungs. The pericardial cavity contained about 20 cc of clear, yellow fluid. There was a fibrous adhesion at the apex of the heart between the visceral and the parietal pericardium occupying an area 1.5 cm in diameter. The heart was enlarged and weighed 630 gm. The left ventricle was markedly elongated, the distance from the mitral ring to the apex of the left ventricle was 10.2 cm, compared to 6.7 cm for the distance from the tricuspid ring to the apex of the right ventricle. The wall of the left ventricle was thickened to 21 mm at the mitral valve, but it tapered to only 4 mm in thickness at the apex. The right ventricle appeared slightly dilated, and the wall measured 4 mm in thickness. The foramen ovale was closed, and there were no interventricular or interauricular defects.

The aortic ring measured 7 cm in diameter. The valve was bicuspid, sclerotic and stenotic, the cusps being stiff and thickened, with rolled edges. There was considerable calcification, especially at the bases of the common coronary cusps and extending into the aortic wall in the sinuses of Valsalva. In addition, a rough, yellow, inverted Y-shaped, hard, verrucous, calcific mass extended down over the left ventricular endocardium from the right coronary cusp. This mass was superficial and did not impinge on the underlying myocardium.

The two coronary cusps were equally small and confluent, with a rudimentary ridge instead of a commissure between them (Fig. 2). Together these cusps measured only slightly

more in transverse diameter than the opposing noncoronary cusp. The rudimentary septum partially dividing the small coronary cusps was smooth and hemispherical and projected 2 mm above the sinus wall. This ridge ran vertically and joined the aorta much lower than the other two commissures, which showed no interadherence between the cusps. In the anterior leaflet of the mitral valve just below the noncoronary cusp there was a rough, atheromatous plaque, which measured 1.5 cm in diameter. The remainder of the mitral valve, together with the pulmonary and tricuspid valves, was entirely normal.

The stiffness of the "double" aortic cusp and the absence of the normal commissure left the coronary orifices completely unprotected, however, the coronary arteries contained only minimal atherosclerotic changes. The right coronary artery had two ostia. The ascending aorta was fairly narrow, measuring 6 cm in circumference. More striking, however, was the marked narrowing just beyond the origin of the left subclavian artery at the point of junction with a very prominent ligamentum arteriosum, which measured 0.6 cm in thickness and 1.0 cm in length (Fig. 3). Here the aorta measured 0.5 cm in diameter for almost 1 cm. Internally, there was a small channel measuring 0.2 cm in diameter through this narrowed portion.

Beyond the point of narrowing the descending portion measured 3.7 cm in circumference. The innominate, left common carotid and left subclavian arteries were almost twice the normal caliber. Similarly, the intercostal arteries were two or three times the normal caliber, and a small linking with associated notching of the ribs was noted laterally in the chest wall. There was thickening of the walls of the larger arteries at the base of the brain, but no atheromatous



FIGURE 3 Gross Specimen of the Great Vessels, Showing Marked Narrowing of the Aorta just Beyond the Prominent Ligamentum Arteriosum

plaques. The remainder of the organs were not especially noteworthy.

Several microscopical sections of the myocardium through the interventricular septum just below the aortic valve in the region of the bundle of His failed to reveal the bundle but showed considerable interstitial fibrosis and coarse myocardial fibers with no inflammatory infiltration. An increase in interstitial fibrous tissue was also noted in the myocardium at the base of the mitral valve. This did not extend into the valve leaflet, nor were similar foci found elsewhere in the myocardium.

Sections taken horizontally through the origin of the abdominal commissure from the aorta and stained for elastic tissue revealed the annulus fibrosus superficial to the media, in the same relation as a normal commissure (Lewis and Grant¹⁹). However, a coronal section taken through the rudimentary ridge just before it joined the aortic cusps and stained for elastic tissue revealed a single delicate elastic lamina running immediately beneath the endocardium, without evidence of fibrosis or inflammation.

BALLISTOCARDIOGRAMS IN COARCTATION OF THE AORTA*

Observations before and after Operation

HERBERT R. BROWN, JR., M.D.,† MARVIN J. HOFFMAN, M.D.,‡ AND VINCENT DELALLA, JR., M.D.‡

ROCHESTER, NEW YORK

THE recent interest in coarctation of the aorta can be attributed to the development of a surgical treatment eliminating the stenotic area.¹⁻³ In recent years the number of reported cases has steadily increased. This apparent increased incidence probably represents a new awareness leading to a much more frequent diagnosis of a condition that was formerly a medical curiosity. The incidence of coarctation as given by Levine⁴ is 0.05 per cent of the population.

In large measure the diagnosis depends first upon thinking of the possibility of this condition and

cerebrovascular accidents are often present terminally.

Early in the course of the disease the symptoms are scant, and clinical findings more important. One should routinely feel for abdominal and femoral pulsations, which are characteristically diminished or absent in coarctation of the aorta. When this

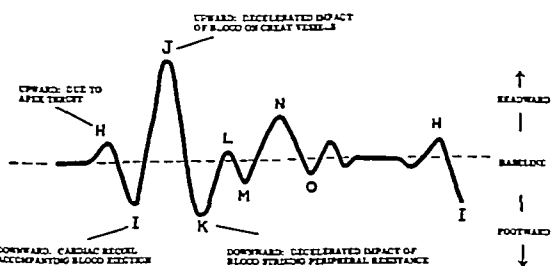


FIGURE 1 Drawing of the Normal Ballistocardiographic Wave Pattern, with a Brief Explanation of the Most Significant Waves

secondly on a few additional procedures indicated to aid in establishing a diagnosis. Coarctation of the aorta must be suspected if a diagnosis of hypertension, rheumatic heart disease or congenital heart disease is made, particularly in young persons.

The patient with coarctation is frequently without complaint. When symptoms are present they can be attributed to impaired circulatory dynamics resulting in an increased pressure above the stenosis. Headache and dyspnea are the two most common symptoms.⁵ On occasion, palpitation, epistaxis, visual disturbances, vertigo, dizziness, intermittent claudication or angina pectoris may be attributed to this abnormality. Symptoms of heart failure or of

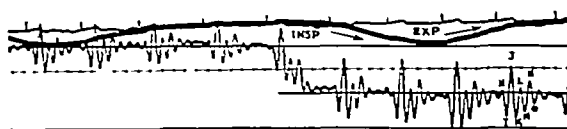


FIGURE 2 Representative Normal Ballistocardiographic Tracing

Note the regularity and definitiveness of the pattern. Simultaneously recorded with the ballistocardiogram are respirations (the heavy, undulating line) and the electrocardiogram. The distance between two heavy time lines is 0.2 second, and that between two fine lines 0.04 second.

abnormality is suspected the blood pressures should be determined in the lower as well as the upper extremities to detect a reversal of the normal relation.

Other clinical features are the demonstration of a collateral circulation, usually over the thoracic, scapular and clavicular areas, the presence of one or more cardiovascular murmurs, roentgenographic evidence, particularly that of rib erosion, and characteristic differences in direct intra-arterial radial and



FIGURE 3 Ballistocardiographic Tracing of a Patient with Hypertension, Demonstrating Deep JK Strokes. This is a common finding in hypertension.

femoral pulsations where the femoral pulse is delayed both in the onset and in attaining its maximum height.⁶

It is the purpose of this paper to add another laboratory measurement that is characteristic of aortic coarctation — namely the ballistocardiogram. Obtaining ballistocardiographic records requires

*From the Department of Medicine, University of Rochester School of Medicine and Dentistry, and the Medical Clinic, Strong Memorial and Rochester Municipal hospitals.

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†Bertha Hochstetter Buswell Fellow in Medicine, Strong Memorial Hospital.

‡Veteran fellow in medicine, Strong Memorial Hospital.

fibrosus at the origin of the congenital ridge. In almost all of Koletsky's cases the elastic strands of the media remained superficial to the annulus until well out in the ridge. In some the annulus fibrosus then became superficial.

Furthermore, the complete lack of inflammatory or degenerative changes in the coronal section through the rudimentary ridge seemed incompatible with acquired fusion as described by Sohval and Gross.¹⁶ This evidence strongly favored the congenital origin of the ridge.

Transverse sections just below the aortic valve through the interventricular septum revealed only dense interstitial fibrosis, and the bundle of His was not identified. This seems to provide an anatomic explanation of the complete heart block. On the other hand, the etiology of this fibrosis remains open to considerable question.

Though the gross picture was compatible with, but not strongly suggestive of, rheumatic endocarditis and aortic valvulitis, no definite microscopical proof of this diagnosis was found. The possibility that the interstitial fibrosis was rheumatic in origin could not be ruled out, however, the lack of other foci of interstitial fibrosis elsewhere in the myocardium and the absence of additional rheumatic stigmas suggested that the local fibrosis was the result of local myocardial strain as in a case (No 7) described by Cohen et al.,¹² which also showed interstitial fibrosis and complete heart block associated with calcareous aortic stenosis without rheumatic heart disease.

The second problem raised by the autopsy was the actual cause of death. Sudden unexplained death in cases of calcific aortic stenosis is not uncommon. Though this case did not show such severe stenosis as the usual fatal cases, the final episode was similar. The lack of any evident anatomic explanation and the known serious disturbance in the cardiac conduction system led us to attribute death in this case to sudden ventricular standstill or fibrillation.

SUMMARY

A case of coarctation of the aorta associated with Adams-Stokes syndrome, complete heart block and a calcareous stenotic bicuspid aortic valve is presented, with post-mortem findings and a brief review of the pertinent literature.

The heart block appeared to be related to the calcific aortic valve and interstitial fibrosis in the region of the bundle of His.

This is believed to be the first case of coarctation of the aorta with Adams-Stokes syndrome and complete heart block reported.

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because of his refusal to partake in gymnasium classes at school

The family and the past histories were noncontributory

Physical examination revealed a slightly obese boy, in apparent good health, who tired easily upon moderate exercise. The abdominal, femoral and dorsalis pedis pulsations were greatly diminished and barely perceptible. The heart was not enlarged, with sounds of good quality. The second sounds were distinct in all areas. A normal sinus arrhythmia was present. There was a loud systolic murmur over much of the

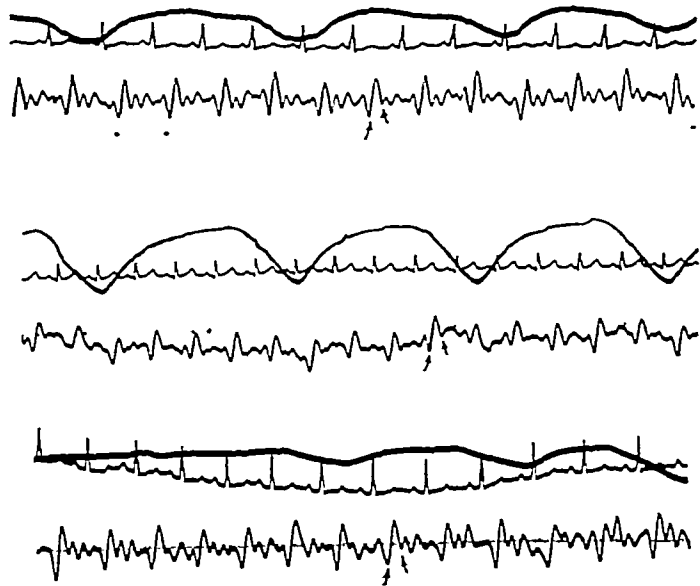


FIGURE 6 *Ballistocardiographic Tracings of 3 Patients with Coarctation of the Aorta, Showing the Short JK Stroke*

cise. The relevant positive findings of this examination included an elevated blood pressure in both arms (right arm, 180/130, and left arm, 170/120). The blood pressures in the anterior portion of the chest, transmitted to the left axillary region and also to the neck. A short early diastolic murmur was heard, well localized to the apex. No thrills were pal-



PREOPERATIVE BALLISTOCARDIOGRAM



POSTOPERATIVE BALLISTOCARDIOGRAM

FIGURE 7 *Ballistocardiographic Tracings before and after Operation. Note the complete return to normal of the entire wax pattern, particularly the disappearance of the short JK stroke postoperatively. (This case is described in detail in the text.)*

legs were not obtainable. A bounding radial pulse was noted, with capillary pulsations visible in the fingers. By contrast, the lungs were clear. No collateral vessels were noted in the usual locations.

but a few minutes and is without discomfort to the patient. The apparatus used is an electronic device that permits simultaneous recording of the electrocardiogram, ballistocardiogram and respirations.⁷

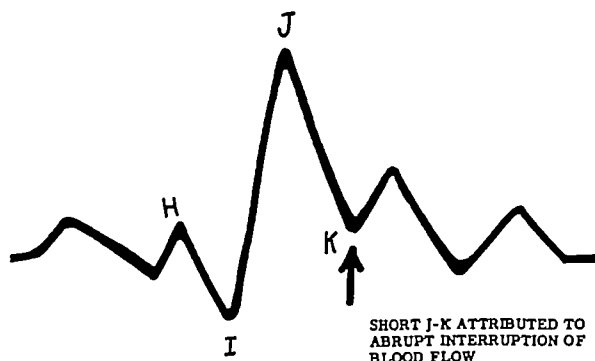


FIGURE 4 Drawing of the Typical Ballistocardiographic Wave Pattern in Coarctation of the Aorta, Characterized by a Short JK Stroke

The ballistocardiogram itself constitutes a simple means of visualizing mechanical circulatory function. Figure 1 is a wave pattern as originally designated by Starr,⁸ with a brief explanation of the sig-

the decelerated impact of blood as it strikes the major peripheral arterial resistance. As would be expected, typical hypertension is normally characterized by a deep JK stroke⁹ (Fig 3). The coarctation, although hypertension is present in the upper extremities, offers an early obstruction to the flow of blood through the aorta, and, again, as would be expected, this early and abrupt interruption results in an abnormally short JK stroke (Fig 4), during and after which blood flows to the lower parts of the body primarily through the well-developed collateral circulation. This was originally mentioned by Hamilton.¹⁰

To date ballistocardiograms have been obtained in 6 consecutive cases in which the diagnosis was firmly established, and the short JK stroke was clearly demonstrated in all (Fig 5 and 6). If the above postulation is correct, surgical removal of the coarctation should restore normal circulatory dynamics, with a resultant typically normal JK stroke. In 1 of these 6 cases of coarctation preoperative and postoperative records that completely support the above conclusion (Fig 7) were obtained.

The case history of this patient was as follows:

A N, an 11-year-old boy, had been under a physician's care since the age of $4\frac{1}{2}$ years, when hypertension associated with a harsh precordial systolic murmur had been discovered. These findings had persisted during the ensuing

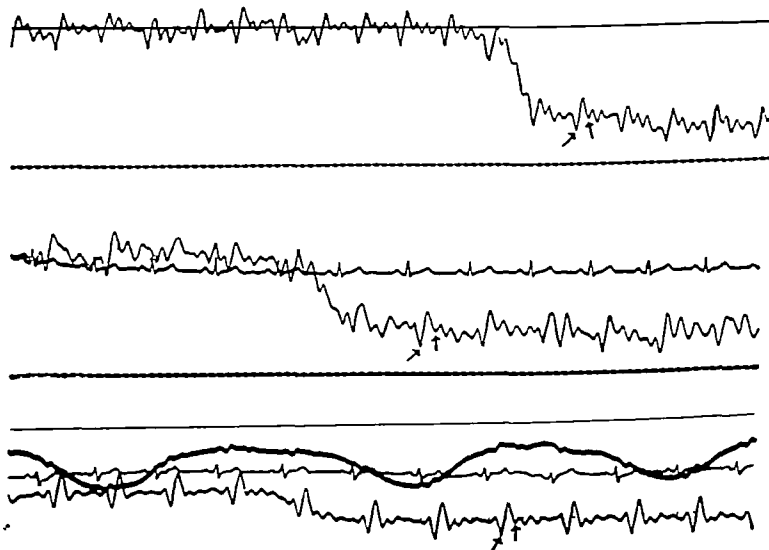


FIGURE 5 Ballistocardiographic Records of 3 Patients with Coarctation of the Aorta in Whom the Diagnosis Was Well Established. Each of these tracings demonstrates the pathognomonic finding of a short JK stroke.

nificance of each individual wave. Figure 2 is a representative normal tracing. In coarctation the K-wave variation constitutes the single purpose of this paper. The JK stroke normally represents

years. His only complaints were dyspnea on running, rare headaches and occasional bouts of mild epistaxis. No history of coma, convulsions, paralysis, eyesight abnormalities or genitourinary complaints was elicited. The patient was finally re-examined 1 year before operation in the hospital.

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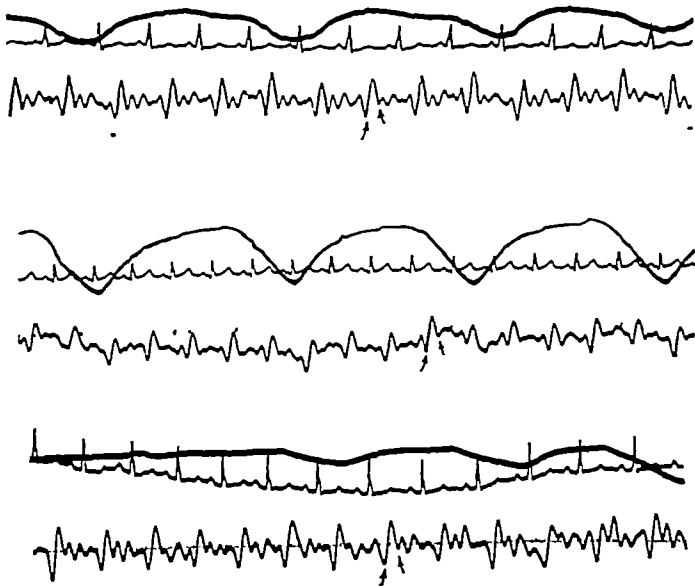
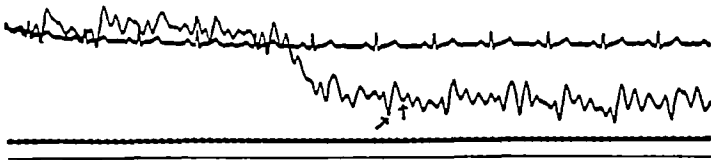


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pable. The lungs were clear. No collateral vessels were noted in the usual locations.

Examination of the blood showed a red-cell count of 4,390,000, with a hemoglobin of 12 gm, and a white-cell count of 10,000, with a normal blood smear, a blood Wassermann test and a urine examination were negative. A urea clearance test was 65 per cent and 70 per cent of normal, the blood urea nitrogen was 14.2 mg per 100 cc, and an intravenous pyelogram was normal. A roentgenogram of the chest revealed a prominent left ventricle, but no suggestive notching of the ribs. Fluoroscopy showed definite and marked pulsations toward the neck of the vessels on both sides of the mediastinum. There was no accentuation of the ascending aorta. An electrocardiogram showed a PR interval of 0.15 second, borderline right-axis deviation, a deep S wave in Lead I and a diphasic P wave in Lead 3.

On March 15, 1947, the preoperative ballistocardiogram was recorded. One year later, surgical correction was successfully accomplished by Dr R. E. Gross in Boston. At operation a point of narrowing was found about 1.5 cm below the aortic arch. At this site the aorta had a tiny lumen, no more than 3 mm in diameter. The narrowed portion of the aorta was removed, and by means of an end-to-end anastomosis the lumen of the aorta was restored to normal size. The patient's general condition was good during and after surgery, and he enjoyed an uninterrupted convalescence.

He has been well since operation. A ballistocardiogram taken on October 2 was entirely normal. The blood pressures at this time were recorded as 118/70 in the left arm and 124/60 in the right arm. Pressures in the legs were 140/60 in both, with a restoration of good pulsations in the abdominal aorta and femoral arteries. The heart murmurs, however, have persisted as before.

SUMMARY

Six consecutive cases of definitely established coarctation of the aorta showed the characteristic ballistocardiographic abnormality of a shortened JK stroke. This demonstrates the usefulness of the ballistocardiogram as a diagnostic agent in suspected cases of aortic coarctation.

In the normal ballistocardiogram there is a full and uninterrupted downward JK stroke, which represents the decelerated impact of ejected blood as it strikes the major peripheral arterial resistance. The abrupt and early interruption of the flow of blood because of the coarctation, then, is the cause of the shortened JK stroke. Surgical correction of this abnormality should restore normal dynamics and produce a normal ballistocardiogram.

The case history and preoperative and postoperative ballistocardiographic tracings of a patient with this condition are presented.

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PRESENT-DAY STATUS OF FENESTRATION SURGERY*

LEIGHTON F. JOHNSON, M.D.,† AND HECTOR SILVA, M.D.‡

BOSTON

THE purpose of this paper is to present a study of the results of fenestration surgery, based on our ten years' experience at the Boston University School of Medicine and Massachusetts Memorial Hospitals, on observations made at various other clinics visited and, finally, on the current literature.

In any discussion of fenestration surgery it should be remembered that the first practical, considerable operation for the relief of deafness from otosclerosis was devised by Dr. Julius Lempert. It is also interesting to observe that the major changes in the evolution of this work have emanated from him. However difficult the birth of fenestration surgery may have been, its value is now generally recognized, and its future secure.

The etiology of otosclerosis is still unknown. There is, however, an immense amount of research being carried on to determine the etiologic factors,

and it appears probable that a plausible explanation for this pathologic phenomenon will soon be described. Such observers as Kobrak, Hallowell Davis, Stacey Guild, Dorothy Wolf and Weaver, working in the allied fields of histopathology, physiology and electronics, have greatly extended otologic concepts, and aural mysticism is beginning to give way to aural realism.

The pathology of otosclerosis is complex and not clearly understood. It is known that the process may appear anywhere in the bony capsule of the labyrinth. It is also known that eighth-nerve deterioration is part of the complex picture of otosclerosis, and no explanation for this phenomenon has thus far appeared. The whole subject is teeming with challenging, unsolved problems. So far, there is insufficient evidence to prove that fenestration of the labyrinth halts the progressive degenerative changes of the eighth nerve. The question whether a successful fenestration operation gives a respite from deafness for ten or fifteen years or whether it is a permanent cure cannot be answered today. Deaf-

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†Professor of otolaryngology, Boston University School of Medicine, chief Otolaryngology Service, Massachusetts Memorial Hospitals.

‡Resident in otolaryngology, Massachusetts Memorial Hospitals.

ened persons, however, are anxious to avail themselves of the possibility of social and economic rehabilitation even if the permanency of the operation is still in question

The selection of cases suitable for fenestration is an exacting responsibility and plays a most important part in the success or failure of this work. To hope to restore hearing to the practical threshold, which is considered to be the 30-decibel level, presupposes a nerve response by bone conduction of 30 or better by audiometric examination and a differential between the air and bone audiogram of at least 25 decibels. This differential between the air and bone response is referred to as the cochlear potential. The tuning forks continue to be invaluable in the diagnosis of otosclerosis and in the selection of suitable cases for operation.

It is true that certain patients with an audiometric nerve response in one or more frequencies below 30 decibels improve remarkably after operation. In many such cases both the patient and operator are conscious of the probability of failure, and occasionally there is a gratifying result. However, we consider the favorable response too infrequent to justify the procedure except in rare cases.

The principle behind the fenestration operation is a delightfully simple one. In brief, the oval window has been invaded by the otosclerotic process, thereby partially or completely shutting out the air-borne sound waves from the labyrinth. The operation calls for the construction of a new window into the labyrinth through which the sound waves may pass. The execution of this simple principle to the ultimate goal of restored hearing is, however, complex and highly technical.

The technic of the fenestration operation is familiar to all. Its evolution embraces two main eras. During the first period, in which the window was made in the external horizontal canal, the incus was left in situ. The immediate results of this operation were spectacular, however, within the first year two thirds of the cases had bony closure of the fistula, and the hearing dropped to the preoperative level. In the present era the fistula is made in the surgical dome of the vestibule, and the incus is removed. This new window has been named the *novalis*. In this location a much larger fistula can be made, and the selection of this site by Lempert doubtless saved fenestration surgery from the discard.

Innumerable attempts have been made to influence the osteogenic reaction around the fistula by a wide variety of procedures ranging from the gold burr, various obturators and cartilaginous stopples to the lead burr. Lempert has proved by experiments on monkeys that the lead burr definitely inhibits osteogenesis. It is now our practice to use the lead burr routinely. The present technic of preparing the fistula by removal of the lid in one piece obviates the production of much bone dust

and thereby lessens the likelihood of bone regeneration.

All aspects of the fenestration operation must be performed with technical finesse, but it is the fistula that requires meticulous endeavor, and success or failure largely hinges on this aspect of the operation.

We believe that progress has been too rapid in the endeavor to handle the difficult problems connected with osteogenesis and fistula patency. Certain procedures that appeared sound from the standpoints of physiology and physics have sharply reduced the percentage of successes — for example, the cartilaginous stopple and the use of the dental excavators. Most operations in which the stopple was employed did not bring the hearing acuity to the practical threshold. The use of the dental excavators stimulated the endosteal layer, with resulting untoward osteogenesis. We are convinced that the present cupola technic of Lempert or the double line procedure of House will give a sharply increased percentage of success in cases reported one or two years hence.

The causes of failure of the fenestration operation include improper selection of cases and bony closure of the fistula. The incidence of bony closure when the fistula is made in the surgical dome of the vestibule by the cupola or twin line technic and properly treated with lead has been reduced to approximately 10 per cent. It should be emphasized that the flap should undergo most careful scrutiny under magnification for the presence of bony spicules. Obviously, if a bony spicule is attached to the under-surface of the flap and the spicule falls over the fenestra, early closure is certain. Revisions when bony closure has reduced the hearing to the preoperative level are far more successful today than in the era of the fistula in the external horizontal canal.

Aseptic labyrinthitis continues to be a possible source of failure. However, with penicillin given routinely for five days, its incidence has been greatly curtailed. Great care must be exercised in irrigation so that the membranous labyrinth is not traumatized while bone dust is being washed away from the endosteum, any instrumentation calls for meticulous effort to avoid trauma to the labyrinth.

Thermal changes to the labyrinth by excessive heat caused by the polishing burr or an irrigation solution that is too warm must be zealously guarded against.

There must be complete hemostasis at the time the labyrinth is opened.

The anesthesia for the fenestration operation seems to vary with each clinic. The following is the anesthetic procedure in use at the Massachusetts Memorial Hospitals.

Preoperative medication should be adequate to provide a good night's sleep and to present the patient in the operating room quite drowsy and euphoric. 2 gm of phenobarbital at bedtime, the

dosage being repeated if necessary for sleep, 2 gm of phenobarbital by mouth at 6 a m, 2 to 6 gm of neonal by mouth at 6 30, 5 to 8 mg of morphine sulfate subcutaneously at 7, and 5 to 8 mg of morphine sulfate and 0.6 mg of atropine sulfate subcutaneously at 7 30.

On arrival in the operating room at 7 45, a needle is inserted in a vein, preferably of the lower extremity, and an infusion of dextrose in water is started. The pharynx is sprayed with 2 per cent pontocaine. Sodium nembutal, in a dosage ade-

quate to induce sleep, is injected into the tubing (50 to 150 mg is usually sufficient). A continuous infusion of 0.4 per cent pentothal sodium is started about five minutes before incision by the insertion of a needle through the tubing so that the solution runs in through the needle previously placed. When the patient is sufficiently relaxed, a Guedel oropharyngeal airway is placed and oxygen is run in through a catheter threaded through this during operation. The total dose of pentothal sodium is usually 1 gm or less, and rarely is as much as 1.5 gm.

TABLE 1 *Results of Novovalis Fenestration Operation in 151 Cases, 1942-1946*

RESULT	PERCENTAGE OF CASES
Practical hearing	60.0
Improved hearing	26.0
Preoperative hearing level	13.0
Hearing worse after revision	0.88

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This anesthesia, in the hands of the Anesthesia Service, has proved safe and satisfactory.

Postoperatively, each patient receives 300,000 units of penicillin daily. Pyribenzamine, in amounts of 50 mg, is given four times a day. This is administered empirically in the hope that its antihistaminic action may prove beneficial in thwarting the possibility of chemical labyrinthitis. The cavity is packed with either paraffin gauze or small sea sponges. We have been using the sea sponges for some time, since they are easy to apply and remove, and are successful in firmly attaching the flap to the bony surface. The packs are removed on the fifth day under careful aseptic technic, and the patient leaves the hospital on the tenth day. Office dressings are done once or twice a week thereafter until the cavity is dry and epidermatized.

Throughout our entire series we have had no mortality and no injury to the facial nerve. There have been no untoward complications such as lateral sinus thrombosis and intracranial disease. The complications have been limited to local allergic reaction to the sulfonamides, a few cases of persistent aural discharge requiring considerable time and patience to dry up, a case of acute otitis media after operation, with spontaneous rupture (with

large doses of penicillin the middle ear became dry, and the perforation healed with no ultimate damage to the improved hearing), and 4 cases of atresia of the external auditory meatus, requiring excision of scar tissue.

The results of fenestration surgery may be divided into four groups as follows: patients who show a postoperative hearing level of 30 decibels or better for the vital frequencies of 512, 1024 and 2048; patients whose postoperative hearing level is not sustained at the 30-decibel level but in whom definite gain in hearing acuity has taken place; patients whose hearing remains at the preoperative level; and those whose hearing has become worse after operation.

Table 1 shows our record at the Massachusetts Memorial Hospitals with the novovalis operation from 1942 to 1946. Any skillful operator can have an immediate record of at least 80 per cent successes, but at least one year should transpire before the permanency of the hearing can be accurately evaluated. It should be mentioned that this list includes 4 cases in which the stopple was employed, none of which reached the practical threshold. Many of the patients listed as improved are perfectly rehabilitated, but since their audiograms do not show the practical threshold of 30 decibels, they are labeled only as improved. Nearly all in this group had practical hearing immediately after operation, but in the year and a half since then, 14 per cent

TABLE 2 *Results in the Experimental Group (Diminished Bone Conduction), 1942-1946*

RESULT	PERCENTAGE OF CASES
Practical hearing	31
Improved hearing	18
Preoperative hearing level	51
Hearing worse	0

have fallen to the preoperative level. Many are suitable for revision.

The second group comprises 32 experimental cases in which one or more of the vital frequencies were below the 30-decibel level by bone conduction (Table 2).

CONCLUSIONS

We believe that no patients with otosclerotic deafness have experienced restored practical hearing except by the Lempert fenestration operation. Several thousand patients today have been socially and economically rehabilitated by this means. In skilled and trained hands the surgical hazards are minimal. The likelihood that further impairment in hearing will result from operation is less than 1 per cent.

The record of the last two years gives every promise of substantial improvement in the per-

centage of practical hearing, because of the improved fistula technic

The work is new and should be approached only by those with broad otologic training and an investigative temperament

In the transition from surgical procedures for infections to operation and study for the alleviation of deafness otology has emerged increased in stature and achieved an enviable position among the surgical specialties

MEDICAL PROGRESS

ORAL SURGERY (Continued)

KURT H. THOMA, M.D.*

BOSTON

DENTOALVEOLAR SURGERY

Dentoalveolar surgery, which includes the extraction of teeth (exodontia), probably occupies a large part of the time of most oral surgeons

The technic of tooth extraction has been perfected. Teeth judged to be complicated on x-ray examination because of exostosis of the roots or anatomic deformity are excised by an open procedure that allows clear vision and prevents laceration of the soft tissue and fracturing of the surrounding alveolar bone.^{51 52}

Much more attention has recently been devoted to the correction of deformities and preparation of the alveolar ridge for the construction of satisfactory dentures.^{53 54} Deformities such as maxillary protrusion are eliminated by alveolectomy. Bony exostoses and hyperplasia of the gums are excised. Irregularities caused by trauma when the teeth are extracted are eliminated to produce an even ridge, and in cases of atrophy of the alveolar process, knife-edge ridges should be made smooth,⁵⁵ whereas in other cases an operation for ridge extension is indicated.^{56 57}

New methods have been developed during the last two decades for the removal of unerupted and impacted third molars. An odontectomy⁵⁸ is performed if the tooth is impacted. This includes tooth division to preserve the bone, large parts of which formerly had to be removed to dislodge the tooth *in toto*. Pell and Gregory⁵⁹ report their findings on the basis of a ten-year study and recommend tooth sectioning highly because of the small amount of operative trauma, which reduces the postoperative discomfort.

It is generally believed that the removal of these malposed teeth can be more easily performed in young persons, and others have gone so far as to recommend prophylactic odontectomy^{60 61} to prevent the crowding and disalignment of anterior teeth. Such malocclusion is caused by pressure of

the third molars in their attempt to erupt. Other reasons for the early removal of these teeth are, according to Gunter,⁶² the following: their eruption may be accompanied by pain and infection of the investing structures (pericoronal infection), they are often hypoplastic and susceptible to dental caries, their repair, if decay is present, is difficult and inadequate, and they tend to disturb the alignment of other teeth. In addition should be mentioned obscure, referred pain, which may radiate to other branches of the fifth nerve or may even involve other nerves of the face and head.⁶³ There is no room in the modern dental arch for third molars, and few of them ever become functional teeth.

The patient's general health and resistance should be considered in case of multiple extraction of infected teeth, and the dentist should consult with the patient's physician.⁶⁴ This is especially true in cases of diabetes and cardiac, thyroid and renal diseases. Most patients with such diseases should be hospitalized, properly prepared and premedicated, and given the protection of antibiotic therapy before and during the operation and also post-operatively. Kane⁶⁵ points out that the danger of bacteremia during the extraction of infected teeth should always be kept in mind. The risk of bacterial shower is present not only in apical abscesses but also in periodontal infection. O'Kell and Elliott⁶⁶ have recovered *Streptococcus viridans* from the blood stream in 75 per cent of 40 patients suffering from marked pyorrhea. Barnfield,⁶⁷ studying autopsy records of 92 cases of subacute bacterial endocarditis, found in 6 a relation between the disease and extraction. Of 40 reported cases supposedly precipitated by dental extraction, in 15 there was convincing evidence, whereas in 10 others the relation seemed probable. Kane⁶⁸ believes that oral surgeons may do much to prevent the occurrence of subacute endocarditis by giving patients with heart murmurs prophylactic penicillin, which is superior to the sulfonamides in preventing transient bacteremia. Pressman and Bender⁶⁹ report an incidence of bacteremia as high as 80 per cent after

*Emeritus professor of oral surgery and Charles A. Brackett Professor of Oral Pathology, Harvard University; lecturer in oral surgery, Graduate School of Medicine, University of Pennsylvania; member, Board of Consultation, Massachusetts General Hospital.

tooth extraction The American Heart Association⁶⁹ has urgently recommended that dentists take advantage of the prophylactic effect of penicillin when extracting teeth for patients with rheumatic heart disease

Patients with a hemorrhagic diathesis require special consideration Hemorrhage following tooth extraction has always been feared though lately great progress has been made in its prevention In many cases, local causes are present, such as fractured alveolar process and lacerations of the gingiva If bleeding is due to systemic disease, a more serious situation exists, and general as well as local therapy is indicated The patient should first of all be hospitalized, and a thorough blood study should be made The following treatment has been recommended⁷⁰

In ascorbic acid deficiency, which is generally recognized because it produces a typical scorbutic gingivitis besides the well known general signs, spontaneous hemorrhages occur in the mouth from the bluish-purple, bloated gums Patients should receive 500 mg of ascorbic acid per day with vitamin P (citric) to decrease the capillary fragility

In thrombocytopenic purpura, splenectomy may almost immediately cause a marked increase in the platelet count, and fresh blood transfusions are valuable In cases of secondary purpura that are not improved by splenectomy in addition to transfusions, the use of moccasin venom has been recommended⁷¹

In cases of pernicious anemia, liver therapy is indicated, in cases of hemorrhage associated with obstructive jaundice, vitamin K with bile salts should be given In the leukemias, blood transfusions to decrease the danger of hemorrhage in preparation for necessary tooth extraction, which should be avoided if possible, are considered helpful In hemophilia, a cure cannot be expected, but in anticipation of tooth extraction, or if the patient has started to bleed spontaneously, transfusions of fresh blood (twelve to twenty-four hours old) are recommended to reduce the coagulation time Small amounts of blood (50 to 100 cc) will reduce the coagulation time markedly Such transfusions should be repeated frequently until the danger of hemorrhage has passed They should be given preoperatively, during the operation and postoperatively

Lewis and his associates⁷² reported that normal plasma contains a substance that is absent in hemophilic plasma and is a subfraction of the active globulin fraction with which it is associated In the Plasma Fractionation Laboratory of the Department of Physical Chemistry, Harvard Medical School, an antihemophilic globulin, Fraction I, of normal blood plasma has been developed for intravenous administration and is provided by the Red Cross without charge It will reduce the coagula-

tion time to about fifteen to thirty minutes after one or two intravenous injections of the content of two vials containing 200 mg each, diluted in 5 cc. of sterile water The tooth extractions should be performed as soon as the clotting time has been reduced to safe ranges, and it is recommended that all the teeth that have to be extracted be removed at one sitting The reduction of the clotting time persists for about four hours, after which it slowly rises to its previous high level The injection may be repeated until the wound has healed completely This treatment, however, has not been found to give uniformly good results, and blood transfusions may have to be given as well It is believed by some hematologists that there is another factor lacking in hemophilia, such as a serum activator, that has not been discovered as yet

Other patients may have a predisposition to hemorrhage that is not so easily recognized Among these are patients with prothrombinopenia, which may arise from lack of vitamin K because of dietary deficiency, faulty absorption due to lack of bile salts (obstructive jaundice, biliary fistula and sprue) or severe infection and liver damage Here should be mentioned the effect of the prolonged use of acetylsalicylic acid, which may decrease the prothrombin Prothrombinopenia may be corrected in such cases by the administration of vitamin K Cahn⁷³ recommends that 1 mg of vitamin K be prescribed to every 0.38 gm of aspirin, if the drug is taken constantly

There is also recognized nonhemophilic hereditary hemorrhage, which occurs in patients with perfectly normal hematologic findings, except the bleeding time, which is prolonged They suffer from prolonged bleeding after injuries, especially the extraction of teeth In some the tourniquet test is positive whereas the platelet count and coagulation times are normal Offspring of either sex may inherit the disease Levy⁷⁴ recently reported 4 such cases with prolonged bleeding after extraction of teeth

Local Treatment of Hemorrhage

Before the local treatment is described, it should be pointed out that patients with or without hemorrhagic diathesis who have been bleeding excessively become dehydrated Fluids should be forced by mouth or given intravenously, or blood should be given if the hemoglobin and red-cell count are low⁷⁵

After the extraction of teeth, meticulous care should be taken to arrest all bleeding from soft-tissue wounds Often suturing is indicated A sterile pack of gauze may be applied between the jaws It is placed on the bleeding socket or on an oozing wound that has been sutured, until the clot has formed Excessive bleeding from a tooth socket may be dealt with by the placing of thrombin or

oxidized cellulose into the alveolus, as described below

In case of secondary hemorrhage after tooth extraction the socket should be debrided, all old clot removed, and a pressure pack applied. The patient should be placed in a semi-Fowler position if in bed, or should be directed to sit in a chair rather than to lie down, to decrease the blood pressure in the head. Cold compresses applied to the region or to the neck are often useful. Rinsing the mouth should be prohibited.

Various drugs have been recommended for local application. Epinephrine in 1:1000 solution is generally employed during operation. The use of ferric subsulfate powder pressed into a socket with iodoform gauze and left for several days has given good results, although the black precipitate is objectionable. In patients with hemorrhagic diseases the bleeding may be arrested by the local application of fresh raw meat, fresh blood or cephalin. Beef or rabbit globulin can be applied on gauze into the socket, and has been recommended as a great aid in such bleeding after tooth extraction. Today, oxidized cellulose⁷⁶ may be left in the wound permanently, avoiding the danger of new hemorrhage, which is always feared when a medicated gauze pack is being removed. I have found thrombodont cones,* which contain 1 unit of thrombin and 1 mg of tyrothricin, extremely effective; they are ideal for use in the mouth because they contain an antibiotic that is effective against gram-positive and some gram-negative organisms found in the oral cavity. One to three are placed into a tooth socket, or if the bleeding occurs at the gingival margin, they can be crushed to a powder and held in place by an intermaxillary pack. These local measures are of great help whether or not general medication and blood transfusions are used.

ODONTOGENIC INFECTIONS

Focal Infection

Chronic dental abscesses and periodontal diseases as foci of infection played an important role three decades ago. Today focal infection is not heard of so much in this country, although abroad papers on this subject are making up a considerable part of the literature. This may be due to the great clean-up that followed the denunciation of septic dentistry by William Hunter in his famous inauguration lecture at McGill.⁷⁷ The American dentist was quick to change his attitude toward the retention of all teeth whether good or bad as long as they were asymptomatic, and discarded practices that led to the formation of abscesses. When it is deemed advisable to retain a tooth in spite of an infected pulp, root-canal therapy is undertaken. Bacterial tests are made during the treatment of

the root canals, which are not filled until they are free of infection.⁷⁸

Reimann and Havens⁷⁹ concluded that the field of focal infection has been definitely narrowed from former concepts. Several sobering articles have appeared to discourage those who believe that all ills can be cured by the extraction of teeth, and it has been pointed out that the removal of a focus of infection presents more prophylactic than therapeutic potentialities.⁸⁰ However, the theory of focal infection should not be entirely discredited since there are still occasional cases in which there is a good probability of the relation of infected teeth to the systemic disorder of the patient. Kravitz⁸¹ believes that, of all foci of infection, those of the teeth are most closely related to the eye. Slocumb et al.,⁸² of the Mayo Clinic, discussing the effect of the removal of foci of infection in heart disease, chronic infectious arthritis and glomerulonephritis (conditions representative of those in which removal of foci of infection has been said to be of clinical benefit), state that in heart disease focal infection can be considered to be a factor only in an occasional case of coronary thrombosis or acute pericarditis. However, they lay stress on the importance of protecting patients by means of chemotherapy when septic tonsils and badly infected teeth are removed in the presence of an old valvular lesion. As previously mentioned, bacteremia following dental extractions may become the starting point for acute bacterial endocarditis. In chronic infectious arthritis, the authors recommend eradication of a definite focus if present after the progression of symptoms is under control. Chronic glomerulonephritis is considered to be caused by repeated and continued toxic assaults on the kidneys originating in acute and chronic foci of infection. Patients with chronic nephritis, intermittent suffering and exacerbations have more than 80 per cent evidence of chronic infections about the roots of teeth, tonsils or sinuses, and clearing up such foci not only shortens the convalescent period of the acute episode but also prevents further damage to the kidney. Ensign⁸³ points out that infected pockets in periodontal disease are an important focus, and the mobility of the teeth aids toxic absorption, "the tooth acting as a piston pumping bacteria into an area of rich capillary supply."

Acute Alveolar Abscesses

These inflammations and their sequelae, deep infections involving the fascial planes around the jaws, have been accompanied with very serious complications. Keefe⁸⁴ called attention to the fact that three periods of disease may be distinguished: that in which the initial lesion develops, that of extension to the fascial spaces, and that of serious complications through embolism, pyemia and septicemia. Havmaker,⁸⁵ of the Army Institute of Path-

*Available from L. D. Caulk Company, Milford, Delaware.

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Patients with a hemorrhagic diathesis require special consideration Hemorrhage following tooth extraction has always been feared though lately great progress has been made in its prevention In many cases, local causes are present, such as fractured alveolar process and lacerations of the gingiva If bleeding is due to systemic disease, a more serious situation exists, and general as well as local therapy is indicated The patient should first of all be hospitalized, and a thorough blood study should be made The following treatment has been recommended⁷⁰

In ascorbic acid deficiency, which is generally recognized because it produces a typical scorbutic gingivitis besides the well known general signs, spontaneous hemorrhages occur in the mouth from the bluish-purple, bloated gums Patients should receive 500 mg of ascorbic acid per day with vitamin P (citrin) to decrease the capillary fragility

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ODONTOGENIC INFECTIONS

Focal Infection

Chronic dental abscesses and periodontal diseases as foci of infection played an important role three decades ago. Today focal infection is not heard of so much in this country, although abroad papers on this subject are making up a considerable part of the literature. This may be due to the great clean-up that followed the denunciation of septic dentistry by William Hunter in his famous inauguration lecture at McGill.⁷⁷ The American dentist was quick to change his attitude toward the retention of all teeth whether good or bad as long as they were asymptomatic, and discarded practices that led to the formation of abscesses. When it is deemed advisable to retain a tooth in spite of an infected pulp, root-canal therapy is undertaken. Bacterial tests are made during the treatment of

the root canals, which are not filled until they are free of infection.⁷⁸

Reimann and Havens⁷⁹ concluded that the field of focal infection has been definitely narrowed from former concepts. Several sobering articles have appeared to discourage those who believe that all ills can be cured by the extraction of teeth, and it has been pointed out that the removal of a focus of infection presents more prophylactic than therapeutic potentialities.⁸⁰ However, the theory of focal infection should not be entirely discredited since there are still occasional cases in which there is a good probability of the relation of infected teeth to the systemic disorder of the patient. Kravitz⁸¹ believes that, of all foci of infection, those of the teeth are most closely related to the eye. Slocumb et al.,⁸² of the Mayo Clinic, discussing the effect of the removal of foci of infection in heart disease, chronic infectious arthritis and glomerulonephritis (conditions representative of those in which removal of foci of infection has been said to be of clinical benefit), state that in heart disease focal infection can be considered to be a factor only in an occasional case of coronary thrombosis or acute pericarditis. However, they lay stress on the importance of protecting patients by means of chemotherapy when septic tonsils and badly infected teeth are removed in the presence of an old valvular lesion. As previously mentioned, bacteremia following dental extractions may become the starting point for acute bacterial endocarditis. In chronic infectious arthritis, the authors recommend eradication of a definite focus if present after the progression of symptoms is under control. Chronic glomerulonephritis is considered to be caused by repeated and continued toxic assaults on the kidneys originating in acute and chronic foci of infection. Patients with chronic nephritis, intermittent suffering and exacerbations have more than 80 per cent evidence of chronic infections about the roots of teeth, tonsils or sinuses, and clearing up such foci not only shortens the convalescent period of the acute episode but also prevents further damage to the kidney. Ensign⁸³ points out that infected pockets in periodontal disease are an important focus, and the mobility of the teeth aids toxic absorption, "the tooth acting as a piston pumping bacteria into an area of rich capillary supply."

Acute Alveolar Abscesses

These inflammations and their sequelae, deep infections involving the fascial planes around the jaws, have been accompanied with very serious complications. Keefe⁸⁴ called attention to the fact that three periods of disease may be distinguished: that in which the initial lesion develops, that of extension to the fascial spaces, and that of serious complications through embolism, pyemia and septicemia. Haymaker,⁸⁵ of the Army Institute of Path-

*Available from L. D. Caulk Company, Milford, Delaware.

ology, has described 27 cases of fatal intracranial complications of dental infection. Direct spread was more often caused by maxillary than by mandibular teeth, whereas in hematogenous infection the reverse was true. Osteomyelitis of the sphenoid bone occurred in 8 cases, brain abscess in 7, cavernous-sinus thrombosis in 9, infraorbital abscesses in 6, and intraorbital abscesses in 3. Hargraves⁸⁶ stresses the need for early and adequate treatment to reduce the mortality by preventing such complications.

The best treatment of acute dentoalveolar abscesses is prompt extraction of the tooth, under the protection of antibiotic therapy. A culture should be taken to establish the penicillin sensitivity of the organisms. Swelling of the face and early cellulitis generally require no treatment besides continuation of parenteral administration of the antibiotic.⁸⁷ In advanced cases when submaxillary, submental, sublingual, parapharyngeal, masseter, parotid and infratemporal abscesses or their complications have already developed, removal of the original focus (tooth) will not afford sufficient drainage, and the antibiotic treatment will not be effective without operative interference.⁸⁷ Incision and drainage should be resorted to, and great care should be taken to open deep accessory abscesses. Since penicillin has come into use, complications are less frequent and less likely to have a fatal result. An example is a case reported by Wiesenfeld and Philipps⁸⁸ of a patient with thrombophlebitis of a cavernous sinus developing after tooth extraction in spite of adequate sulfadiazine administration, who made a dramatic recovery after the administration of penicillin (150,000 units a day). Ludwig's angina also has a much better prognosis, since penicillin has given striking results in early cases with and without incision.⁸⁹

Bacteriologic examination is of great importance since mixed infections are very common in the mouth. Colon bacilli, gram-negative organisms and especially the fusospirochetal organisms are frequently found accompanying infections by the streptococcus or staphylococcus, and in some cases the use of streptomycin is therefore indicated. Actinomycosis frequently yields to penicillin therapy. Nichols and Herrell⁹⁰ reported cures in 24 out of 26 cervicofacial cases. They recommend the administration of 500,000 units daily for six weeks.

OSTEOMYELITIS OF THE JAWS

The treatment of osteomyelitis of the jaws, which may be caused by dental infections and septic fracture, occasionally by furunculosis⁹¹ and through hematogenous transportation of bacteria,⁹² has also undergone a considerable change since the advent of chemotherapy.

Infantile Osteomyelitis of the Maxilla

This condition has a better outlook. Intramuscular injections of penicillin, 80,000 to 800,000

units a day, are recommended and, if an intraoral fistula is present, should be supplemented with penicillin irrigations.⁹⁴ Schenk⁹⁵ described 5 patients all of whom recovered in spite of a mortality of 20 to 50 per cent. He recommended that penicillin should be administered promptly, and a minimum of 800,000 units should be given over a long period. Sometimes, penicillin combined with sulfonamide is recommended in mixed infections.

Osteomyelitis of the Jaws in Adults

This inflammation occurs in an acute fulminating form and the more frequent subacute and chronic types. The former is often aborted if penicillin treatment is instituted even before x-ray evidence of bone changes can be demonstrated.⁹⁶ In most of the subacute and chronic cases the use of antibiotics and the removal of the cause do not result in resolution without operative interference to eliminate pus and necrotic tissue since patients frequently do not seek treatment until extensive suppuration and bone necrosis have occurred.⁸⁷ Various operative procedures performed under antibiotic therapy are recommended,⁹⁷ including surgical drainage, sequestrectomy and saucerization, fixation in pathologic fracture and very rarely excision of the affected segment of bone. Sequestrectomy is simple if an intraoral approach is possible, frequently, however, the sequestrum is encased or inaccessible, and an extraoral sequestrectomy is recommended.⁹⁸ This is combined with careful débridement and saucerization of the bone defect. Excision (condylectomy) is especially indicated if the infection is restricted to the condyloid process, which occurs as a complication of an infratemporal abscess, since osteomyelitis here generally causes partial or complete ankylosis of the mandibular joint.⁹⁹ In any of these procedures intramuscular administration of antibiotics should be supplemented by local instillation of a solution of 1000 to 5000 units of penicillin per cubic centimeter into the involved area, as recommended by Smith-Petersen, Larson and Cochran.¹⁰⁰ A rubber catheter sutured to the margin of the incision gives satisfactory results and allows primary closure of the wound.

The determination of the bacteria causing the infection is recommended in each case, with their sensitivity to specific antibiotics. Although staphylococci and streptococci are the common bacteria found, Vincent's organism, colon bacilli and many other aerobic and anaerobic organisms may be encountered. It is well to have a serologic test because syphilis occasionally simulates pyogenic osteomyelitis,¹⁰¹ and in the localized form tuberculosis should be kept in mind.¹⁰² Pathological examination of the excised tissue establishes the diagnosis.

Good postoperative care is of great importance in osteomyelitis. This includes a liquid diet high in protein, caloric and vitamin content. The adminis-

tration of fluids and electrolytes is indicated, and the use of blood transfusions to improve the patient's general resistance aids the recovery

Irradiation Osteomyelitis

Necrosis of the jaw, as well as a slowly progressing sclerosing type of osteomyelitis, is produced by heavy irradiation for the treatment of cancer. The resorptive and regenerative power of the bone is destroyed. Watson and Scarborough¹⁰² reported on 235 cases of osteonecrosis found in a group of 1819 patients with cancer of whom 12 died free of cancer as a direct result of jaw infection. Colby¹⁰⁴ makes a statement with which I thoroughly agree — namely, that radical dental treatment is indicated before irradiation, all remaining teeth being extracted. Irradiated patients on the other hand should have no operative procedures on the irradiated jaw for years. If teeth remain, proper hygienic conditions should be maintained, and extremely conservative dental treatment is imperative. The use and construction of protective prostheses containing lead shields has been described by Ackerman¹⁰⁵. They are used to protect the regions of the jaw that are not to be irradiated.

FRACTURES OF THE MAXILLA AND MANDIBLE

Great progress was made in the treatment of fractures of the jaws during World War I, but there were certain limitations, which were only recently overcome with the advent of the use of antibiotics. Simplified methods of fixation that require less technical work (dental splints) have been developed,¹⁰⁶ assuring more rapid results with less discomfort to the patient. This refers particularly to transosseous wiring and skeletal fixation.

Transosseous Wiring

While the use of open reduction with internal wiring fixation has been discouraged in the past, Gordon¹⁰⁷ reported the use of this method for 7 malar, 2 maxillary and 15 mandibular fractures. Adams¹⁰⁸ described a method of fixation for maxillary fractures by wiring the fractured parts to neighboring unfractured bony structures to avoid uncomfortable extraoral appliances such as headbands and plaster caps. The prophylactic use of penicillin and of stainless steel or tantalum wire, which are biologically inert, probably plays a great part in the recent success with these methods. It is, however, important not to rely on the wires for the immobilization of jaw fractures. The wire should serve only to hold the fragments in the reduced position so that they cannot be displaced by muscle pull. The fracture should be fixed by immobilization of the mandible.¹⁰⁹

Indications for transosseous wiring are mandibular fractures at the angle of the jaw with upward or lateral displacement of the posterior segment,

fractures through an unerupted third molar, which should be removed, and comminuted fractures with small displaced segments.

Transfixation with Steinmann Pins

This method is hazardous because it easily causes injury to the inferior alveolar nerve and vessels, resulting in anesthesia of the lip and intraosseous hematoma. However, it is useful¹¹⁰ in fractures of the symphysis, as well as for craniomandibular fixation. This method and others eliminating the use of headbands and plaster caps were described by Thoma.¹¹¹

Skeletal Pin and Clamp Fixation

Numerous advantages are claimed for this method. Winter,¹¹² in a report on 36 cases, stated that skeletal fixation made early and prompt reduction possible, since it required a minimum of complicated equipment and therefore could be applied in dressing stations, field hospitals, evacuation hospitals or on shipboard. Of first importance in war surgery, he stated, was the fact that with this method the soldier with a mandibular fracture may be transported after the fracture has been reduced without danger to his life from sea or air sickness. Secondly, because the bone is immobilized but the joint is free, moderate function is possible, which is a great advantage not only because it provides better nourishment for the patient, eliminating the preparation of liquid diets, but also because it favors healing. Haynes¹¹³ pointed out that callus formation may be expected earlier because it is known that the use of a bone increases the inflowing calcium and counteracts the atrophy that occurs from disuse. Other writers pointed out additional advantages. Mowlem et al.¹¹⁴ stated that the method facilitated oral hygiene, simplified feeding and prevented stiffness of the joint and muscles. Griffin¹¹⁵ added that drainage, inspection and irrigation were easily made in compound fractures and fractures with extensive wounds. Gillies¹¹⁶ stressed the perfect control of the fragments into which the pins were inserted and the easy anatomic positioning.

The indications for the use of skeletal fixations were set down by Waldron.¹¹⁷ He recommends the method for badly displaced fractures of the edentulous mandible, particularly when they are comminuted, fractures behind the angle of the jaw, when the posterior fragment becomes difficult to maintain in reduced position, multiple fractures involving both the upper and the lower jaw, when other methods are not satisfactory because of the loss of teeth, comminuted fractures of the mandible with destruction of a section, and cases in which facilities for construction of dental splints are not available.

Thoma¹¹⁸ found skeletal fixation unsatisfactory for cases of fractures at the angle of the jaw, pins will not hold well or last, because the bone in this

part of the mandible is very thin. He developed a peripheral bone clamp that can be placed around the jaw through a suitable incision in the skin, which is closed. Only the pin protrudes through the skin and serves as an attachment for the connecting bars of the fracture appliance fastened to half pins inserted in the anterior fragment.

Bradford and Wilson,¹¹⁹ discussing skeletal fixation, give two good rules to prevent misuse or abuse of the method: the apparatus should be applied only by an experienced surgeon who thoroughly understands the principles of its use and who has carefully studied its mechanism, and the procedure should not be used routinely but should be applied only in cases in which treatment by simple, conservative methods seems to be inadequate.

Fractures of the Mandibular Condyle

These fractures, treated in the past by immobilization of the mandible without any attempt at reduction, have not given such uniformly good results as some of the proponents of conservative treatment suggest. In cases of gross displacement or fracture dislocation this treatment frequently results in deformity, functional debility and malocclusion with deviation on opening of the mouth, and ankylosis may occur.¹²⁰⁻¹²² A method of education and wiring fixation is recommended to prevent these deformities.¹²³ If they do occur, condylectomy will have to be resorted to to give relief.¹²¹

In conclusion, it may be said that the treatment of jaw fractures requires a great deal of experience with a variety of methods old and new. In a discussion of the history of the treatment of jaw fractures¹²³ some of the principles regarded as essential have been set forth and discussed. These are as follows: treatment of the patient, attention to soft-tissue wounds, carefully performed clinical and x-ray examination, determination of the type and exact location of the fracture, prevention and treatment of infection, temporary immobilization if adequate treatment has to be delayed, choice of the correct type of anesthesia, attention to proper reduction, selection of the best method of fixation and immobilization, and proper attention to after-care.

DISEASES OF THE MANDIBULAR JOINT

Arthrosis

Various intra-articular changes may occur in the temporomandibular joint owing either to major trauma causing injury to the meniscus or to trauma resulting from functional disturbances,¹²⁴ some of which are distinctly associated with occlusal abnormalities of the teeth. Other diseases that cause similar symptoms are the rheumatoid, hypertrophic and infectious forms of arthritis, which produce degenerative changes similar to those produced in

other joints of the body, and ankylosis of the jaw may result.

Bellinger¹²⁵ describes the symptomatology as follows: the symptoms are usually preceded by a history of a snapping sound in the joint, which may occur at the beginning or termination of the opening movement and is directly related to the meniscus. It indicates hypermobility and excessive excursion. In addition, more or less profound and palpable tenderness, pain and restriction of motion may develop. Extirpation of the meniscus effects immediate cessation of the symptoms.

Other symptoms, reflex in nature, may be experienced. These are generally spoken of as the "Costen syndrome." Besides the noise in the joint during mastication, the patient complains of various forms of neuralgia, such as headaches about the vertex and occiput, pain behind the ear or in the mouth and jaws and a burning sensation or pain in the tongue. Wright¹²⁶ pointed out that deafness may occur, vertigo and tinnitus (noises, buzzing and roaring) may be present, according to Goodfriend.¹²⁷ The dental signs are unusual attrition or loss of or incorrect replacement of the posterior teeth.

The treatment in many cases may be conservative, consisting of resting the jaw and the use of heat. Rest may consist of the omission of food that requires force to masticate, or intermaxillary wiring for complete immobilization. Heat may be applied by means of flaxseed poultices or diathermy. In some cases restoration of the occlusion or wearing of a splint to open the bite and distracting the joint surfaces give good results.¹²⁸ Operative treatment consists of injection of a sclerosing solution, meniscectomy and condylectomy or osteoarthrotomy.

Injection

Injection of the joint space with a sclerosing solution (sodium psyllate or synlasol) is recommended by Schultz¹²⁹ for hypermobility, but not if the patient has acute symptoms, limited motion and pain. Clicking, grating and popping have been controlled in six to twenty-four hours.

Meniscectomy

Meniscectomy is indicated in recurrent dislocation, fracture or tear of the meniscus due to trauma, partial erosion of the meniscus in traumatic arthritis, blocking of the condyle and noise and cracking not relieved by conservative treatment.¹³⁰ Boman¹³¹ reported 58 cases of treatment by excision of the meniscus.

Condylectomy and Osteoarthrotomy

These operations are used in more serious disease of the mandibular joint, destruction of the joint surfaces with resulting pain, as in various forms of arthritis, in partial ankylosis caused by traumatic

arthritis, malunion of condylar fracture, rheumatoid arthritis, osteomyelitis of the condyle and hypertrophy (osteoma) of the condyle and true ankylosis. The causes of ankylosis⁹⁹ are birth trauma, rheumatoid arthritis, including Marie-Strümpell disease, suppurative arthritis, osteomyelitis of the condyle and fracture of the condyle with hemarthrosis.

Dingman¹³² and Thoma⁹⁹ prefer osteoarthrotomy to arthroplasty since there is less chance of recurrence because of the large separation of the condylectomized ramus from the glenoid fossa or temporal bone (1.5 to 2.0 cm). Hickey¹³³ has experimented with oxidized cellulose (oxycel), which he packs into the space not only because it controls the bleeding but also because it is said to interfere considerably with bone repair.¹³⁴

(To be concluded)

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Condylectomy and Osteoarthrotomy

These operations are used in more serious disease of the mandibular joint, destruction of the joint surfaces with resulting pain, as in various forms of arthritis, in partial ankylosis caused by traumatic

was slightly elevated, and the hemoglobin was essentially normal. The sedimentation rate was elevated and indicated that infection was present. The calcium and phosphorus were normal, as was the phosphatase. May we see the x-ray films?

DR STANLEY M WYMAN: The lesion, I think, is readily seen on this view of the pelvis, which shows both upper femurs. The left femoral shaft, just below the lesser trochanter, shows an area of marked cortical, possibly some periosteal, thickening with a focus, perhaps 1.5 cm., of sharply defined rarefaction (Fig 1). This is better seen on slightly more exposed films and is shown in both projections. This view shows what was called a periosteal calcification, apparently separated from the tendon, at least, in part. There is no definite evidence from these films of any focus of increased density within the ovoid rarefaction. There is no evidence of ray formation and no evidence of a soft-tissue mass.

DR DALAND: The severity of the symptoms was not very great apparently at this time, and after staying in the hospital for ten days and carried only on aspirin, she was sent home. It must have been believed that there was nothing suggesting a tumor at this time, or I think she would not have been allowed to go home. In looking at these films we see a heaping up of calcification by periosteal replacement of bone, which does not look like tumor formation. One would think that if a Ewing tumor were present, we might get a heaping up here of the so-called onion-skin appearance. We would also have a soft-tissue mass, and the appearance of the bone would be unlike this. We would not expect to find a hole in the bone.

She was sent home and returned eight months later. In the interval she continued to go to school, so that the pain could not have been very severe. The pain persisted in the medial aspect of the upper third of the thigh and was more constant at rest, disappearing on activity. The symptoms recurred regularly at 2 a.m. and were entirely relieved by aspirin. This type of pain at night is rather typical of bone pain. We find it in joint disease as well. The classic story of the child with a tuberculous hip or knee is that of a patient who is fairly comfortable in the daytime but has pain at night. In this case there is nothing else to suggest a joint condition. At night there is complete relaxation of muscles, but the patient moves in bed and awakens with severe spasm that brings on pain.

We have, then, a girl with a low-grade condition, pain over a period of eighteen months plus eight months, a little over two years. During that time she was able to carry on and go to school, and the pain did not increase a great deal. Have we the films of the last admission?

DR WYMAN: We have only the films of the first admission. The others have disappeared, unfortunately. There was essentially no change, however

DR DALAND: The duration and type of pain pretty much rule out neoplastic disease in the early examinations. We know that she had an elevated sedimentation rate. It was indicated at one time that she had a considerable degree of infection somewhere. The normal calcium, phosphorus and phosphatase help rule out any type of cystic disease from hyperparathyroidism. The appearance of this lesion was not that of a solitary bone cyst. That is usually a central, medullary condition running down the canal and not showing an overgrowth



FIGURE 1

of bone like this, unless there has been a fracture. We do have evidence of a good deal of periosteal proliferation and overgrowth, but more important is the area that was hollow in the center of the reactive bone. This is the sort of thing that one gets in a bone abscess or Brodie's abscess. In Brodie's abscess the pain is low grade and may continue for a number of months without being severe enough to call for any operative treatment. It is rather unusual to find it in the femur. It is much more common in the tibia but is occasionally found in the fibula. This is the age at which one is pretty apt to find a Brodie abscess, anywhere between twelve and twenty—it is rarely seen in adults. I think we can

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

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CASE 35181

PRESENTATION OF CASE

First admission A fourteen-year-old girl entered the hospital complaining of pain in the left hip for eighteen months

Ten months before admission the patient had an attack of "streptococcal sore throat" and was confined to bed for two weeks During this period she noticed an intermittent, dull ache in the left hip, present usually at night After getting up, the pattern of symptom-free days and pain at night persisted The pain was relieved by aspirin The sedimentation rate was at first normal and later found to be elevated

Physical examination demonstrated no abnormalities except for tenderness over the left femur anteriorly at the level of the lesser trochanter There was no limitation of hip motion

The temperature, pulse and respirations were normal The blood pressure was 105 systolic, 70 diastolic

Examination of the blood disclosed a white-cell count of 10,800, with 68 per cent neutrophils, and a hemoglobin of 13.8 gm per 100 cc The urine was normal The erythrocyte sedimentation rate was 30 mm in one hour The blood calcium was 9.1 mg, the phosphorus 3.9 mg and the alkaline phosphatase 3.1 units per 100 cc A blood Hinton test was negative

X-ray study revealed a dense area of periosteal new-bone formation associated with the medial anterior aspect of the proximal femoral shaft (Fig 1) This periosteal new bone was in part differentiated from the course of the bone In the lateral view a circular zone of rarefaction was observed in the cortex at about the midportion of the area of new-bone formation

The patient received aspirin on several nights for relief of pain, and was discharged ten days after admission

Second admission (eight months later) In the interval she continued to go to school The pain persisted in the medial aspect of the upper third of the left thigh, more constant at rest and disappearing on activity It recurred regularly at 2 a m and was entirely relieved by aspirin She took up to 8 aspirin tablets daily There was no recorded temperature elevation at home

On physical examination the findings were unchanged from those on the previous admission In the left thigh, about 9 cm below the anterior superior spine and 1.2 cm medially, was an area of deep tenderness, measuring 5 by 5 cm No mass was palpable The range of motion of the joint was full There was 1.2 cm of measurable atrophy of the left thigh, 15 cm above the patella

An operation was performed

DIFFERENTIAL DIAGNOSIS

DR ERNEST M DALAND This was a low-grade type of pain Apparently it had been that for a number of months We are told that it started eighteen months previously and that ten months before admission the patient had a streptococcal infection We know nothing about what happened at the onset of this disease eighteen months before admission, but at one time apparently she did have an infection that laid her up in bed for two weeks The sedimentation rate was found to be normal, and as time went on it was elevated She had definite tenderness over the upper femur The temperature was normal when recorded The white-cell count

tion and was given oral fluids and insulin. On the day before entry another physician aspirated some material from the right eye.

For approximately sixteen years the patient had mild polyuria and polydipsia but refused to see a physician. For five to ten years she had occasional ulcers on the lower legs that occurred on the slightest trauma and were very slow to heal. In the two years before admission she had intermittent pain and injection of the right eye, with decreased vision and marked photophobia.

The patient's mother had diabetes for many years. Her father and two brothers died of carcinoma. One sister had a "lump" removed from a breast. The patient's husband was in a tuberculosis sanatorium fifteen and again eight years previously, each time for approximately a year.

Physical examination revealed an obese, critically ill woman. The right conjunctiva was injected, the globe was prominent, and the eye was very tender. The skin was hot and dry. There were a few necrotic lesions on the toes that looked like small areas of gangrene underlying old calluses. Examination of the chest was unsatisfactory owing to poor cooperation, but nothing significant was found. The heart was not enlarged, and a Grade II to III, harsh, high-pitched systolic murmur was heard over the entire precordium, loudest at the apex and toward the sternum. No diastolic murmur was heard. The sounds were of good quality. The abdomen was huge, with a thick panniculus. The dorsalis pedis and the posterior tibial arterial pulsations were not felt. There were scarred and pigmented areas over the lower extremities.

The temperature was 103.6°F, and the pulse 100. The blood pressure was 140 systolic, 70 diastolic.

The urine had a specific gravity of 1.026 and gave a + test for albumin. The white-cell count was 24,900, with 91 per cent neutrophils. The hemoglobin was 16 gm. The blood sugar was 279 mg. and the nonprotein nitrogen 39 mg. per 100 cc. and the carbon dioxide 27 milliequiv. per liter. An x-ray film of the chest showed increased vascular markings throughout both lung fields. At the right apex there was a rounded area of increased density. The aorta was somewhat tortuous. The heart appeared to be somewhat enlarged, with left ventricular prominence. The spinal fluid contained 5 lymphocytes and 210 red cells per cubic millimeter. The protein was 45 mg. per 100 cc. The gold-sol curve showed elevation in the mid-zone to a maximum of 2. A blood culture taken on admission grew out beta-hemolytic streptococci in both flasks.

The patient received 1,500,000 units of penicillin a day. On the first day of hospitalization she received a total of 90 units of insulin. The temperature dropped to normal, but the fasting blood sugar remained elevated to 346 mg. per 100 cc. The chemosis in the right eye increased and the process

was thought to be a hemorrhagic glaucoma. The ocular tension was 37 as compared to 20 in the left eye. She had immature cataracts in the left eye. She continued to have a fever of 100°F to 101°F and a white-cell count varying from 18,000 to a maximum of 27,000. The sensorium cleared somewhat. She received, in addition to the regular injection of penicillin, 25,000 units of penicillin subconjunctivally. There was questionable change in the quality of the heart sounds. On the seventh hospital day it was noted that she was icteric. A Grade I, apical, high-pitched systolic murmur was present, together with a short, high-pitched, coarse systolic sound, best heard in the third left intercostal space but audible at the apex. This second sound was faint and followed shortly by another coarse, high-pitched sound similar to the one following the first sound. There was a questionable, low-pitched mid-diastolic murmur heard at the apex. There was no edema, rash or petechiae, and the spleen could not be palpated. An electrocardiogram showed partial auriculoventricular block, with a PR interval of 0.25 second. The ST segment was slightly elevated in Leads 1, 2 and 3 and V₄, and the voltage was slightly low. On the eleventh hospital day auricular fibrillation was noted. There was a change in the quality of the heart murmurs, a definite low-pitched, rumbling diastolic murmur now being present. The heart rhythm later became more regular, with occasional ectopic beats. The temperature remained nearly normal, though the white-cell count was very much elevated. The icterus became more evident. On the twelfth hospital day she lapsed into coma, breathing became shallow, the blood pressure was unobtainable, and she died.

DIFFERENTIAL DIAGNOSIS

DR. W. WILSON SCHIER. The first significant statement in the history is that this patient was admitted to the hospital because of a fever. Presumably we are dealing with an infectious process from this point on. The low-back pain is mentioned frequently as a cardinal symptom, but my opinion is that this was associated with septicemia. She was acutely ill for ten days preceding hospital admission, and two days before admission she was found to have sugar and acetone in the urine, for which she was given fluids by mouth and injections of insulin.

From the data given I think we are justified in making a diagnosis of diabetes mellitus. This metabolic defect led to a complicated series of events. She apparently suffered from occasional ulcers on the lower legs which were a product of poor circulation. It was noted that arterial pulsations in the posterior tibial and dorsalis pedis arteries could not be felt—consistent with atheromatous degeneration. The character of the walls of the vessels was not commented on. These areas of ulceration

rule out any type of tumor here. I am pretty certain it is infection. At some time she may have had a low-grade osteomyelitis, and this may have been a residuum of it. The other thing that she might have had was a subperiosteal hematoma, the result of some trauma, although we have no note of such trauma. That would give a heaping up of periosteum like this, but probably would not cause the central hollow in the bone. My opinion is that this was a Brodie abscess.

DR WYMAN: Would Dr. Daland consider the possibility of osteoid osteoma, whatever that is?

DR DALAND: Yes.

DR ROBERT S. PALMER: What is it?

DR WYMAN: I do not know.

DR JACOB LERMAN: Were the indications for operation at the second admission any greater than those at the first admission?

DR TRACY B. MALLORY: No, except that she had not improved, and it was obvious that the lesion would not clear up of its own accord.

CLINICAL DIAGNOSIS

Osteoid osteoma

DR DALAND'S DIAGNOSIS

Brodie's abscess of femur

ANATOMICAL DIAGNOSIS

Osteoid osteoma of femur

PATHOLOGICAL DISCUSSION

DR MALLORY: This lesion was explored as is so generally necessary in establishing a diagnosis of a bone lesion. The area of thickening of the periosteum just below the lesser trochanter was found. The cortical bone underlying this area of periosteum was chiseled out, and in the center of the cortical bone a little focus was found, which is shown in this picture (Fig. 2). On the right is the external surface of the cortex, showing irregular thickening beneath the area of periosteal proliferation. In the picture on the left we see the cavity lying within the excised piece of cortical bone. This cavity was filled with a tumor-like mass of material that was rather firm, although distinctly softer than the surrounding cortical bone. Microscopically it was typical of so-called osteoid osteoma. It consisted of interlacing trabeculae of imperfectly calcified osteoid material, and there was the usual increased density of the surrounding cortical bone. Exactly what this lesion was is doubtful as may have been guessed from the questions already asked. Jaffe,* who first described the lesion in 1935, considers it to be a neoplasm of benign character, an unusual feature for neoplasm, however, is that these tumors appear to be entirely self-limited as to growth. In spite of the fact that this had been present two

years and under observation many months between the first and second examinations, there was no increase in size during that time. That is characteristic of similar lesions kept under observation for even longer periods. So, if it was a neoplasm, it was one that is incapable of growth beyond a certain very definite and relatively small limit of size. They always lie in the cortical bone. In this case a narrow, recognizable shell of cortical bone separated the lesion from the medullary cavity, and it was not necessary to enter the medullary cavity to remove

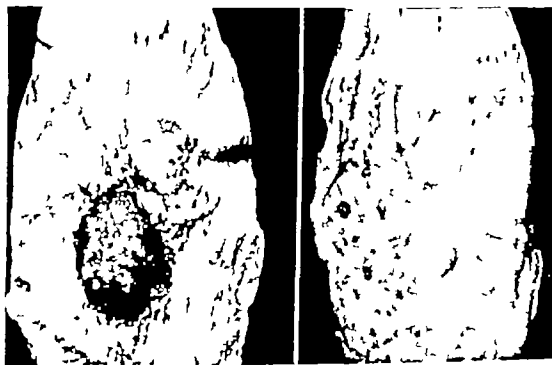


FIGURE 2

the lesion. Very persistent pain is extremely characteristic of all examples of the lesion. Sometimes the pain is more severe than that in this case and may be resistant to much stronger therapy than aspirin.

CASE 35182

PRESENTATION OF CASE

A forty-eight-year-old married woman was admitted to the hospital because of pain in the right eye and fever.

Ten days prior to admission the patient began to complain of low-back pain. Two days after this, the pain having subsided, she became nauseated and vomited while riding in a train. On the following day, seven days before admission, she complained again of low-back pain and was found to have a temperature of 104°F. She refused to see a doctor, though she did take three penicillin tablets, which had been left for another patient. The fever allegedly subsided but returned. She continued to have a high temperature and low-back pain until three days before entry, when the right eye became inflamed. Two days before admission, despite her objections, a physician was called. He found her to be quite ill, tested some urine and found it to contain sugar and acetone. She refused hospitaliza-

*Jaffe, H. L. Osteoid-osteoma, benign osteoblastic tumor composed of osteoid and atypical bone. *Arch. Surg.* 31:709-728, 1935.

at all. Old rheumatic heart disease need not be postulated and the only evidence for a congenital lesion is the description of the murmur heard on admission, which could be consistent with an interventricular septal defect. Were there any evidences of embolic phenomena occurring in the kidney—red cells in particular? The urine is mentioned as showing only albumin. Both focal and diffuse nephritis may be associated with acute endocarditis.

DR MALLORY No red cells were observed in four specimens examined.

DR SCHIER I wonder if anyone would discuss the electrocardiographic changes?

DR JOHN W. HURST The electrocardiogram showed a partial heart block, the PR interval was 0.27 second, the ST segment was slightly elevated in Leads 1, 2, 3 and V_4 with low voltage. I reported that as consistent with myocarditis if pericarditis could be ruled out. It looked more like myocarditis than coronary-artery disease.

DR SCHIER The electrocardiographic changes are consistent both with severe infection and coronary-artery disease or rheumatic fever. The changing rhythm might occur with all of these, particularly the last two. With coronary-artery disease I would expect the ST segments to be depressed. Pericarditis associated with endocarditis and myocarditis would be more apt to cause elevation of the ST segments.

It is said that the patient died in icterus, although none was noted on admission. This seems most likely to have been a result of overwhelming sepsis of the liver from infected emboli. Without further clinical and laboratory evidence I cannot rule out cholelithiasis, pancreatitis and hepatitis. There is no mention of cardiac failure, which could cause jaundice, or evidence of large free emboli. Hemochromatosis is unlikely without the finding of pigmentation. Liver disease usually precedes diabetes by months, and I mention it only in passing.

In summary, my diagnoses are diabetes mellitus, acute endocarditis involving the aortic and mitral valves, septicemia, atheromatous arteriosclerosis, hemorrhagic glaucoma of the right eye and possible cardiac enlargement, with terminal hepatitis.

DR RICHARD CLARK What type of endocarditis? Do you mean acute bacterial endocarditis?

DR SCHIER Yes, acute bacterial—I cannot rule out rheumatic.

DR CLARK Would the appearance of the murmurs in addition to the prolonged PR interval indicating myocarditis together with the ST segments and sounds suggestive of pericarditis as well, fit better with activation of an acute rheumatic process, along with bacterial endocarditis? It is not infrequently seen in combination.

DR SCHIER I do not know.

DR HURST One point that might be brought up concerns the diastolic murmur which you thought might be aortic. Perhaps you were misled by the description in the protocol. That murmur was not of the high-pitched type heard in aortic regurgitation; it sounded more like the scratching of pericarditis. The really changing murmur was at the mitral area rather than the aortic.

DR SCHIER That would change my opinion of the aortic lesion and would be more consistent with a mitral valvulitis.

DR MEANS I think that Dr. Schier has covered nearly everything and I believe our line of thought ran similarly to his. I think he quite properly stressed the changing character of the auscultatory findings in the heart. They changed during observation quite strikingly, and there was one period, I am not sure it got into the record, when there was a most amazing phenomenon. There was only one heart sound, a loud clear sound and nothing else, and that, as well as the septic fever, made us all think that something fairly active must be going on in the heart. We considered the possibility of some kind of pyemic process with pus formation in various places. I do not want to say too much about that because I am vague about our ideas, whether they were before autopsy or after autopsy, but we were concerned about why penicillin did not have more effect. We wondered if it was because she had pus that it could not reach.

This woman was an interesting one from the point of view of personality. She had a strong anti-doctor complex, and we thought that a good deal of her pitiable condition might have been prevented if she had consulted a doctor twenty years previously. The obesity was tremendous and had a good deal to do with the diabetes. She neglected the infections and so forth.

DR ALFRED KRAVES Did the blood cultures become negative after treatment started?

DR MEANS I cannot remember, I think they did.

tion were a likely portal of entry for the subsequent infection. Buerger's disease is described as occurring rarely in women, and its first sign may be migrating phlebitis. It is much more reasonable to assume that the defective circulation was associated with this patient's diabetic state. She had three penicillin tablets preceding admission, and the remote possibility that a refractory organism resulted from this is only mentioned to condemn inadequate medication. She had gangrene of the toes, which is a common complication of untreated mild diabetes.

Is there anything in the record indicating the nature of the aspirated fluid from the right eye?

DR JAMES H. MEANS: I do not know. She was sent to the Eye and Ear Infirmary.

DR SCHIER: I do not know what to make of the eye lesion — I shall accept the diagnosis of hemorrhagic glaucoma. In the absence of other embolic processes it seems barely possible that she had a mycotic aneurysm of the optic artery to account for her symptoms in the right eye. She had had symptoms in the eye, however, during the two years preceding admission to the hospital, which would be consistent with glaucoma.

I now come to the portion of the discussion that offers richer speculative material. The heart initially was described as not being enlarged on physical examination, but a harsh high-pitched systolic murmur was heard over the entire precordium, loudest at the apex and at the sternum. My inclination is to explain the murmur by dilatation of the left ventricle, although old rheumatic fever cannot be dismissed. In addition to the murmur she had a high temperature, and a blood culture grew beta-hemolytic streptococci. The infection was not overwhelming enough to depress the bone-marrow function, for the white-cell count initially was 24,900, with 91 per cent neutrophils. The heart is described on x-ray examination as being enlarged — may we see the x-ray films?

DR STANLEY M. WYMAN: This film was taken with the patient supine and with the x-ray tube quite close to her, therefore, the apparent enlargement of the heart is not valid because of magnification and because of the relatively high position of the diaphragm. Also, the chest is rotated on the film, so that I think it is not safe to make any conclusion at all about the heart size from this examination. There is probably some calcification in the aortic arch seen at that point. The mention

of density at the right apex I am not able to confirm, and I am not impressed by the prominence of the hilar pulmonary vascular shadows in this type of film.

DR SCHIER: You do not see any calcification in the region of the aortic and mitral valves?

DR WYMAN: I do not believe that calcification in that area would show in this type of film, and she was not fluoroscoped. We do have films of the skull that are very fragmentary because of her condition, I assume, but there is a suggestion on two of these films of a calcified vessel seen through the right orbit and lying in the expected location of the internal carotid artery. This may represent a calcified vessel, but I am unable to be certain of the observation from these poor films.

DR SCHIER: That knocks the props from explaining the murmur by left ventricular dilatation. I suppose arteriosclerosis in the valves would explain the murmur.

The lesion at the right apex might well have been tuberculous — in the welter of symptoms and signs a sputum examination may have been overlooked, and we know that tuberculosis is four or five times more common in diabetic patients than in the population at large.

The patient received massive doses of penicillin, which brought her temperature down only temporarily. I assume that the spinal tap was done to rule out possible meningitis. Was the globulin or the gold-sol curve elevated? What did the culture show?

DR TRACY B. MALLORY: No globulin is reported.

DR JAMES WYNGAARDEN: The culture was negative.

DR SCHIER: No further mention is made of blood cultures. On the seventh day there was a change in the quality of the heart sounds. First the development of an aortic systolic murmur, a faint second sound and an aortic diastolic murmur. These events and the evidence of septicemia lead me to conclude that this patient developed an acute endocarditis of the aortic valves. The mid-diastolic murmur at the apex became definite four days later and may have been the result of involvement of the mitral valves by the same process or an Austin-Flint murmur associated with the aortic-valve incompetence — resulting from vegetations or perhaps actual perforation of the valves by the destructive process. Why was the heart involved

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THE HEALTH PROTECTION CLINIC

DIFFERENT projects have been underway for varying lengths of time whereby the person interested in his health problems may undergo a "screening" technic to eliminate, so far as possible, the presence of certain diseases. It seems logical that proposals should be made to amalgamate these screening processes—for cancer, for heart disease, for diabetes, for tuberculosis and for other diseases—under one roof and at one time, for what they are worth.

It is difficult to evaluate this worth on a statistical basis. The most objective mathematician would hardly dare to set an exact price on the saving of a life, and screening technics are capable not only of discovering an uncertain proportion of per-

sons with incipient disease out of the total number examined, but of assuring many of the others of their general good health at the time of examination.

The screening technic itself must naturally not be overrated nor the object of too much enthusiasm. The course of disease may be inexorably progressive or it may first become discoverable after the technic of discovery has declared the patient to be apparently physically fit. Nevertheless, much more can be done to eradicate incipient disease or to mitigate its course than was possible a decade ago.

An objective to be achieved if the health protection clinic is to serve its purpose is that of streamlining its technic. If the processes of discovering the presence or absence of disease are to be made possible on a large scale, they must be so simple that the whole plan does not fall from the sheer weight of man hours involved.

If health protection services, moreover, are to be offered freely or in any other manner to the public, social and economic problems must be settled. Whether the means test, as either an indignity or a dignity, is to be employed must be decided. The method of reference of patients to the clinics and the disposition of them after screening must be determined, as well as the financing of the whole enterprise. The interests of the private practitioner must be protected at all costs, for he is still and will remain the most effective and the most highly considered dispenser of health services.

In this respect it may be pertinent to observe that improvements in health services, as they have generally been offered, have seemed usually to rebound to the advantage of the practitioner. Obviously the health protection clinic as a public service is social medicine. Whether it represents also socialized medicine is a matter of definition, but if it does, the country has enjoyed or suffered under socialized medicine to some degree and in various forms for a number of years.

The important point is that if the practice of medicine continues to change its form, as it has been doing since the Babylonian physicians first added liver divination to their prognostic armamentarium, its course will be truer and its benefits greater if the medical profession goes with it and guides it, and

DR MALLORY Only that single culture is reported

CLINICAL DIAGNOSES

Acute bacterial endocarditis
Cholemia
Diabetes mellitus

DR SCHIER'S DIAGNOSES

Diabetes mellitus
Acute endocarditis, mitral
Septicemia
Atheromatous arteriosclerosis
Hemorrhagic glaucoma of right eye
Terminal hepatitis

ANATOMICAL DIAGNOSES

Endocarditis, acute bacterial, of mitral valve
Abscesses, multiple, of heart, spleen and kidneys
Portal cirrhosis of liver, post-necrotic type
Pulmonary tuberculosis, active, right apex
Patent ductus arteriosus
(Diabetes mellitus)
Arteriosclerosis, generalized, moderate

PATHOLOGICAL DISCUSSION

DR MALLORY Autopsy confirmed the diagnosis of bacterial endocarditis. When the pericardium was first opened we found a small amount of fresh blood but no inflammatory changes to indicate an infectious pericarditis. On inspecting the surfaces of the heart, we noted several small superficial abscesses, one of which immediately adjoined a coronary vessel, the surrounding tissues were ecchymotic, and we thought there had been a little leakage of blood from the coronary artery to account for the blood in the pericardium. The mitral valve showed a very large shaggy vegetation extending almost two thirds around the orifice. The chordae tendineae were nearly normal—possibly slightly thickened. The annulus of the mitral valve

showed calcification, and there probably was a slight underlying old rheumatic heart disease. The ductus arteriosus was found to be still patent. At the pulmonary end it measured nearly 1 cm in diameter but as it approached the aortic orifice it narrowed markedly and the opening into the aorta measured only 1 mm in diameter. I do not believe a significant amount of blood was passing through and doubt that any of the murmurs were explained on that basis, they probably all arose from extensive mitral involvement. Both infarcts and pyemic abscesses were found in various organs. In the spleen there was one bland infarct and one septic one. There were multiple abscesses in the kidney but no characteristic infarcts. The liver showed a severe degree of cirrhosis of the coarsely nodular, post-necrotic type, and there were demonstrable varices in the lower portion of the esophagus. We found no gross abscesses in the liver, but, on microscopical examination, numerous foci of sepsis were found and I think the combination of old liver disease and scattered fresh necrosis constituted adequate explanation of the terminal liver insufficiency. One large, well encapsulated tuberculous focus was present at the apex of the right lung.

We did not have permission to examine the head.

DR KRANES Did the post-mortem cultures grow the same organisms that were found during life?

DR MALLORY We grew a pure culture of beta-hemolytic streptococci from one of the heart abscesses. Cultures from the kidney grew mixed organisms, both beta-hemolytic and alpha-hemolytic streptococci and colon bacilli.

DR MEANS Could penicillin have been responsible for the colon bacilli? Do they not come in when penicillin is administered?

DR MALLORY They do in open lesions such as bronchiectatic cavities but I do not believe they do within the tissues of the body.

mycin has produced all the toxic effects observed with streptomycin.⁶ In animals it has been found that the acute toxicity—that is, the amount that is fatal for an animal in a single dose—is essentially the same for both compounds.^{4, 5} The histamine-like effect obtained from one lot of dihydrostreptomycin was only about a sixth of that produced by the lot of streptomycin from which it was derived.⁴ In chronic toxicity experiments dihydrostreptomycin proved to be less toxic, in that larger doses given over a longer period were required to produce neurotoxic effects equivalent to those obtained from streptomycin.⁶ There was also some indication that the local ulceration and induration resulting from dihydrostreptomycin in animals were less marked than those produced by streptomycin.

The effects of the use of dihydrostreptomycin in the treatment of human beings have thus far been reported in only a small number of patients, some of whom were treated with impure materials.¹⁰⁻¹³ The results in these cases indicate that dihydrostreptomycin produces all the toxic effects that have been observed from streptomycin. Dihydrostreptomycin, however, may have somewhat less neurotoxicity. The impression gained from the few cases thus far studied after the use of large doses of dihydrostreptomycin is that the vestibular damage occurs later and less uniformly and may be less disabling than that after streptomycin.

The most striking observations, however, have been made in patients who have been unable to tolerate streptomycin because of fever, rashes or other evidences of sensitization. In such patients dihydrostreptomycin has been well tolerated, and it has been possible to continue the treatment of such patients without ill effects.^{5, 13} Some of the experiences with early lots suggested that dihydrostreptomycin was more irritating locally, particularly when given intrathecally.¹² By the latter route streptomycin was said to be preferable,¹³ although the irritation observed from the intrathecal injections of dihydrostreptomycin may have been the result of the use of impure preparations. Dihydrostreptomycin has shown the same tendency as streptomycin to produce resistant organisms and neither compound is effective in the treatment of infections with streptomycin-resistant organisms.⁹

It therefore appears that dihydrostreptomycin may prove useful in the treatment of patients who show allergic sensitivity reactions to streptomycin. It may also prove to be more desirable than streptomycin in patients who require large doses or prolonged treatment as in the therapy of tuberculosis. Further experience is necessary before even these conclusions can be justified.

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INDIAN GIVER

THE Great White Father, despite bumper budgets of recent years, has turned out to be, in the case of his copper-colored children, an Indian giver. The original possessor of the country's fields and forests, now one of the world's most forgotten displaced persons, surrendered these possessions (after a struggle) for the opportunity of living in squalor as a permanent Guest of the Nation.

In both 1947 and 1948, according to *Washington Report on the Medical Sciences*, teams selected by the American Medical Association and sponsored by the Department of the Interior inspected Indian reservations in the West and found appalling conditions of health and living. The Bureau of Indian Affairs of the Department of the Interior then asked for a "minimum needs" budget of \$9,163,814, from which the Budget Bureau promptly slashed \$1,500,000.

Medical Director Fred Foard, protesting both the budget cut and conditions that make it impossible

does not try simply to interpose inadequate obstacles in its path

It seems reasonable that pilot studies at least should be made in the establishment of health protection clinics. From the lessons that they teach new bearings can be taken to guide progressive medicine on its course

GROUP HEALTH ASSOCIATION

TEN years ago in Washington, D. C., bitter controversy arose regarding the so-called Group Health Association, and much opposition to its activities was encountered. Time has passed and views have changed, and elsewhere in this issue of the *Journal* a report appears of the first ten years of that organization, about whose activities there was such a wide difference of opinion at that time regarding its ethical and legal status.

Statistics may be a notoriously unsound basis for the drawing of conclusions, and it is important to note that the author himself states that at least one reason for the fact that the mortality rates compared very favorably with those from the community at large may be that the group so covered was in a higher financial bracket than some other groups. However, the average family income of the group studied would hardly, in these days, be considered much above the lines drawn by various insurance companies to separate those in low income brackets from those in the medically indigent class.

One of the criticisms often made of the attitude of the medical profession is that it has been slow to do anything in the way of constructive planning to meet the needs of present conditions. It is with this criticism in mind that the *Journal* is publishing the article in question, which deals with the experience of a small group in a specific area in the country. It is important to appreciate that it is the *local* physicians who should be in control of the *local* needs of any community, whatever the means or agency may be that attempts to provide good medicine at a cost within the range that the individual can pay. If state and federal aid is needed — and it seems likely that it will be — such aid must not predicate jurisdiction over the *local* needs and problems.

How to co-ordinate local, with general over-all supervision is the question that is fundamental to success.

DIHYDROSTREPTOMYCIN

DIHYDROSTREPTOMYCIN, a new derivative of streptomycin, has recently become available. It is made from salts of streptomycin by a process of catalytic hydrogenation that adds about one molecule of hydrogen to each molecule of streptomycin.^{1,2} The resulting dihydrostreptomycin salts appear to be more stable than the parent compounds in that, unlike the latter, they are not inactivated by cysteine, hydroxylamine or semicarbazide and are not degraded by heating with alkali. Comparative tests of the activity of dihydrostreptomycin and its parent streptomycin have shown that both have essentially the same activity in vitro against most bacteria.^{2,3,4-7} Against some species or strains of organisms, including occasional strains of tubercle bacilli and of salmonella, the dihydrostreptomycin, weight for weight, may be only two thirds or even as little as a fourth as active as streptomycin.^{4,5} In no case has a dihydrostreptomycin compound been found to be more active than its parent streptomycin.⁵ The antibacterial actions of dihydrostreptomycin and streptomycin are similarly affected by changes in pH⁴ and in certain components of the medium.^{4,8} Organisms resistant to streptomycin are equally resistant to dihydrostreptomycin.^{4,6,7} Some workers have suggested that the antibacterial activity of dihydrostreptomycin results from its being oxidized to streptomycin by bacteria.⁹

In animal experiments^{4,5,10} and in man^{10,11} both compounds appear to be absorbed and excreted in essentially the same manner. They appear to be about equally active, weight for weight, against infections in animals with strains of tubercle bacilli^{5,6,7,12} and with most of the pathogenic organisms that have been tested.^{1,4,5} The parent streptomycin, however, appears to be more active on a weight basis against some of these infections.⁵ Dihydrostreptomycin has no therapeutic effect on infections of animals with organisms that are resistant to streptomycin.^{6,7}

The only therapeutic advantage of dihydrostreptomycin has been in toxicity, although dihydrostrepto-

found that the admixture of semen with urine, blood, urethral secretion, sputum, sweat, lachrymal fluid, milk, tea, coffee and cocoa had no deleterious effect upon the phosphatase activity. Likewise, penicillin or sulfathiazole did not affect the phosphatase activity. Dried stains retained activity for several months.

Evidence of the presence of semen on a garment in a case of rape, obtained by the use of the acid phosphatase test, has so far been introduced in the Superior Court in Massachusetts on only one occasion. There is, however, little reason to doubt that the test will be used frequently, and no difficulty is anticipated in having such evidence accepted by the Court, provided it is introduced by a qualified expert.

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It is important that correct registration be completed, because the physician is liable to a fine up to \$100.00 for not so registering, the town or city clerk is liable to a fine up to \$15.00 for each physician not registered by him, and, I am informed, should a physician in this status be involved in court proceedings, should be adequate in all other respects, and should even successfully defend himself in a malpractice suit he would not be entitled to the protection of the law because he was practicing medicine illegally.

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Greenfield, Massachusetts

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Being a New Hampshire "Yankee" myself, I feel doubly proud to know that a New England group has sponsored the publication of thoughts such as these, which are so greatly needed.

EDWARD H. ROBINSON, 1949

Jefferson Medical College

BOOK REVIEWS

Medullary Nailing of Küntscher. By Lorenz Böhler, M.D. First English edition, revised by the author. Translated from the eleventh German edition by Hans Tretter, M.D. 4th, cloth 386 pp., with 1261 illustrations. Baltimore: Williams and Wilkins Company, 1948. \$7.00.

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Sterility and Impaired Fertility. Pathogenesis, investigation and treatment. By Cedric Lane-Roberts, C.V.O., M.S., F.R.C.S., F.R.C.O.G., Albert Sharman, M.D., Ph.D., M.R.C.O.G., Kenneth Walker, M.A., M.B., B.C. (Cantab.), F.R.C.S., F.I.C.S., B.P. Wiesner, D.Sc., Ph.D., F.R.S.E., and Mary Barton, M.B., B.S. 8th, cloth 400 pp., with 96 illustrations and 18 tables. New York: Paul B. Hoeber, Incorporated, 1948. \$6.50.

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The authors are British, and the printing was done in Great Britain and the book bound in the United States. The publication is excellent in every way. A good legible type is well printed on a coated paper. A number of appendices, a long bibliography and a good index conclude the volume. The book is recommended for all medical libraries as a standard reference work and to all persons interested in the subject.

to provide the country's quarter of a million reservation Indians with good medical and public-health care, plans to fight for "reforms of a system in which field medical officers are wholly subordinate to lay commissioners, salaries of doctors and nurses are inadequate and central direction is impossible"

These wards of the state are obviously permanently displaced, perhaps a little more of the nation's charity might begin at home

MASSACHUSETTS MEDICAL SOCIETY

DEATH

HANNIGEN — Robert C Hannigen, M D, of Amesbury, died on December 16. He was in his seventy-second year.

Dr Hannigen received his degree from Medical School of Maine, Portland, in 1901.

His widow, three sons and a daughter survive.

NOTES FROM THE MEDICAL EXAMINER

ACID PHOSPHATASE TESTS AS EVIDENCE OF RAPE

The family physician is usually the first person called when aid or advice is sought by the victim of a sexual assault. His duties in such cases include both the care of the patient and the accumulation of evidence likely to be of value in establishing identity or guilt of the assailant. The evidence is two-fold: that of physical violence suffered by the victim, as shown by bruises, scratches, or other injuries of her body, and evidence of ejaculate on or about her body. Since rape of a child or woman not under the influence of drugs or submitting from fright is practically impossible without leaving marks of violence on the extremities or genitalia, the absence of such injuries casts serious doubts on the fact of the alleged rape even though semen may be demonstrated.

The identification of spermatozoa in stained smears from the victim's perineum or vagina is obviously the best proof of the presence of semen. Identification is usually made on material from four sources: vaginal content, water suspensions of material clinging to the perineum or thighs, soiled pubic hair and stained clothing. In the first two instances smears should be made and dried promptly. The specimens should be submitted in dust-protective wrapping to a laboratory for staining and study by an expert.

Direct demonstration of spermatozoa is frequently impossible, owing either to destruction of the cells in the vagina or their absence in the ejaculate (aspermia or vasectomy). The survival of spermatozoa in the vagina after coitus varies from thirty minutes to twenty-four hours.¹ The phosphatase

test, because it does not depend on intact sperm cells, is a useful adjunct in the study of material suspected of representing ejaculate. The specimens to be collected are clothing bearing stains possibly due to semen, and if feasible, aspirated fluid vaginal content. Stains should be dried, fluid should be refrigerated in a sterile container until testing is done.

Determination of acid phosphatase as a test for seminal stains on clothing was first described by Lundquist and Rasmussen in 1945, and extensive studies by Rüsfield² and Hansen appeared in 1946. The procedure is based on the fact that ejaculate contains a large proportion of prostatic fluid and therefore a high concentration of acid phosphatase derived from prostatic glandular secretion. The demonstration of this enzyme consists of several steps.

Preparation of a saline extract of the dried stain or dilutions of the vaginal content. In stained cloth, the areas to be tested may be selected under ultraviolet illumination, which causes semen as well as many other biologic fluids to fluoresce.

Determination of the acid phosphatase activity of the saline extract by measurement of the phenol released by an aliquot of the extract from a phenylphosphate substrate in one hour under controlled conditions.³

Calculation of the acid phosphatase activity of the original specimen in units per cubic centimeter. This is accomplished directly with liquid specimens and in the case of dried stains by application of a factor that relates area of dried stain to cubic centimeter of original fluid causing that stain. The latter procedure is derived from experiments in similar samples of cloth using milk as the fluid, since the spreading power of milk is similar to that of semen.⁴ One unit of acid phosphatase activity is that of 1 cc of original fluid that will hydrolyze 1 mg of phenol in one hour at pH 4.9 and 37° F.

The acid phosphatase content of all body fluids other than prostatic secretion is less than 20 units, whereas that of ejaculate varies from 400 to 8000 units per cubic centimeter and is high even in the presence of azoospermia or aspermia.² Dried stains or fluid found to contain more than 100 units per cubic centimeter of original fluid are interpreted as indicative of the presence of semen in the specimen.

The technic has gained favor in medicolegal investigation, since it allows the recognition of semen long after the ejaculation or assault has occurred. Rüsfield² demonstrated increased phosphatase activity corresponding to the content of semen in vaginal fluid six and twelve hours after coitus but not after twenty-four hours. He

found that the admixture of semen with urine, blood, urethral secretion, sputum, sweat, lachrymal fluid, milk, tea, coffee and cocoa had no deleterious effect upon the phosphatase activity. Likewise, penicillin or sulfathiazole did not affect the phosphatase activity. Dried stains retained activity for several months.

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OFFICERS OF THE MASSACHUSETTS MEDICAL SOCIETY, 1948-1949

DR. ARTHUR W. ALLEN, *President-Elect**White Star*

PROGRAM OF THE ONE HUNDRED AND SIXTY-EIGHTH ANNIVERSARY OF THE MASSACHUSETTS MEDICAL SOCIETY

Monday, Tuesday, Wednesday and Thursday, May 23, 24, 25 and 26, Worcester Memorial Auditorium and Hotel Sheraton, Worcester

The Registration Desk will be located on the Stage of the Auditorium, and all who attend the meeting are requested to register

MONDAY AFTERNOON, MAY 23

- 4:30 Supervising Censors' Meeting (ROOM E, HOTEL SHERATON)
6:00 Cotting Supper for Councilors (BALLROOM HOTEL SHERATON)

8:55 *A Motion Picture Entitled "Dermatoses of Industrial Workers"*

9:30 *A Public-Health Heart Program — First Report* DR. EGON E. KATTWINKEL, Newton Chief of cardiology, Newton-Wellesley Hospital Drs VLADO A. GETTING, ERNEST M. MORRIS, H. M. LOMBARD and LEWIS C. ROBBINS

9:55 *The National Health Service — Recommendations of the Hoover Commission* DR. HUGH R. LEAVELL, Boston Professor of public-health practice, Harvard School of Public Health



Bachrach

DR. DANIEL B. REARDON, President



Fasch

DR. DONALD MUNRO, Vice-President

MONDAY EVENING, MAY 23

- 7:00 Annual Meeting of the Council (BALLROOM, HOTEL SHERATON)

TUESDAY MORNING, MAY 24

First General Session

LITTLE THEATER, WORCESTER MEMORIAL AUDITORIUM
DR. JOHN J. DUMPHY, Chairman
DR. BAYCROFT C. WHEELER, Co-chairman

10:20 *Compulsory Health Insurance Is this the Best Way to Improve Medical Care?* DR. FRANK H. LAHEY, Boston Director, Lahey Clinic.

11:00 Annual Meeting of the Massachusetts Medical Society (LITTLE THEATER, WORCESTER MEMORIAL AUDITORIUM)

Annual Oration (following annual meeting) Some Responsibilities of Medical Education DR. C. SIDNEY BURWELL, Brookline Dean, Harvard Medical School

Annual Luncheon (following annual oration) tickets must be procured in advance of the meeting

TUESDAY AFTERNOON, MAY 24

Second General Session

LITTLE THEATER, WORCESTER MEMORIAL AUDITORIUM
DR EDWARD P BAGG, *Chairman*
DR DONALD MUNRO, *Co-chairman*

- 2 00 *Pitfalls in the Diagnosis of Diarrhea* DR HUGH TATLOCK, Northampton Staff physician, Cooley-Dickinson Hospital, consultant in medicine, Veterans Administration Hospital
- 2 15 *Pitfalls in the Diagnosis of Continued Fever* DR FRANKLIN K PADDOCK, Pittsfield Attending physician, Pittsfield General Hospital
- 2 30 *Pitfalls in the Diagnosis of Persistent Cough* DR PAUL R DUFAULT, Rutland Superintendent, Rutland State Sanatorium
- 2 50 *Evaluation of the Papanicolaou Technic in the Diagnosis of Malignant Disease* DR HOWARD ULFELDER, Winchester Clinical associate in surgery, Harvard Medical School, assistant surgeon, Massachusetts General Hospital, senior surgeon, Pondville Hospital
- 3 15 *The Present Status of the Management of Thyroid Disease* DR GEORGE CRILE, JR., Cleveland, Ohio Department of Surgery, Cleveland Clinic
- 3 40 *Hospital Administration as a Medical Specialty* DR T STEWART HAMILTON, Newton Director, Newton-Wellesley Hospital
- 4 05 *Observations on Reduced Incidence of Embolism Postoperative ambulation dicumarol routine* DR JAMES C McCANN, Worcester Senior surgeon, St Vincent Hospital
- 4 30 *A Motion Picture Entitled "Anomalies of the Bile Duct and Blood Vessels"*

TUESDAY EVENING, MAY 24

BALLROOM, HOTEL SHERATON

- 8 15 **Worcester Hofbrau Night** (Free beer, free entertainment and music at the invitation of the Worcester District Medical Society)

WEDNESDAY MORNING, MAY 25

Third General Session

LITTLE THEATER, WORCESTER MEMORIAL AUDITORIUM
DR GEORGE R DUNLOP, *Chairman*
DR FRED H ALLEN, *Co-chairman*

- 8 50 *A Motion Picture Entitled "Management of the Failing Heart"*

Symposium on Gastric and Duodenal Ulcer

- 9 25 *Medical Aspects* DR SARA M JORDAN, Boston Director, Department of Gastroenterology, Lahey Clinic, physician, New England Baptist Hospital and New England Deaconess Hospital
- 9 50 *The Roentgenologist's Contribution* DR JOHN D CAMP, Rochester, Minnesota Professor of radiology, Mayo Foundation, consultant in roentgenology, Mayo Clinic
- 10 15 *The Management of Hemorrhage* DR BURRILL R CROHN, New York City Consultant in gastroenterology, Mt. Sinai Hospital, consultant, Veterans Administration, Halloran Hospital, Staten Island, New York

- 10 40 *The Surgeon's Point of View* DR JOHN D STEWART, Buffalo, New York. Professor of surgery and chairman of the Department of Surgery, University of Buffalo School of Medicine.

WEDNESDAY MORNING, MAY 25

LITTLE THEATER, WORCESTER MEMORIAL AUDITORIUM

- 11 05 **The Shattuck Lecture** *La médecine du coeur*

DR PAUL D WHITE, Boston Clinical professor of medicine, Harvard Medical School, consultant in medicine, Massachusetts General Hospital, executive director, National Advisory Heart Council

WEDNESDAY NOON, MAY 25

Section Meetings and Luncheons

12 00 m — 2 00 p m

Section of Medicine

STAGE, WORCESTER MEMORIAL AUDITORIUM

DR LAURENCE B ELLIS, Cambridge, *Chairman*
DR ALLEN S JOHNSON, Longmeadow, *Vice-chairman*
DR JAMES A HALSTED, Dedham, *Secretary*

Therapeutic Advances in the Treatment of Diarrheal Disturbances of Inflammatory Origin DR BURRILL R CROHN, New York City Consultant in gastroenterology, Mt. Sinai Hospital, consultant, Veterans Administration, Halloran Hospital, Staten Island, New York

Section of Pediatrics

ASSEMBLY ROOM, WORCESTER MEMORIAL AUDITORIUM

DR W BRADFORD ADAMS, Springfield, *Chairman*
DR GERALD N HOFFEL, Boston, *Secretary*

Problems of Pediatric Radiology DR EDWARD B NEUBAUER, Cambridge Radiologist, The Children's Hospital, Boston

Section of Radiology

MALE CHORUS ROOM, WORCESTER MEMORIAL AUDITORIUM

DR ALBERT M MOLONEY, Boston, *Chairman*
DR LAURENCE L ROBBINS, Boston, *Secretary*

Significant Roentgenologic Findings in Intracranial Disturbances DR JOHN D CAMP, Rochester, Minnesota Professor of radiology, Mayo Foundation, consultant in radiology, Mayo Clinic.

Section of Physical Medicine

MUSICIANS' ROOM, WORCESTER MEMORIAL AUDITORIUM

DR DAVID C DITMORE, Boston, *Chairman*
DR ARTHUR L WATKINS, Boston, *Secretary*

Rehabilitation of the Patient with Hemiplegia DR WILLIAM B SNOW, New York City Assistant professor of medicine, Columbia University, College of Physicians and Surgeons, director, Department of Physical and Occupational Therapy, Columbia Presbyterian Medical Center

WEDNESDAY AFTERNOON, MAY 25

Fourth General Session

LITTLE THEATER, WORCESTER MEMORIAL AUDITORIUM

DR DONALD B CHEETHAM, *Chairman*
DR LAWRENCE R DAME, *Co-chairman*

- 2 00 *Pitfalls in the Diagnosis of Backache* DR CHARLES E AYERS, Worcester Orthopedic surgeon, The Memorial Hospital
- 2 15 *Pitfalls in the Diagnosis of Rectal Bleeding* DR E PARKER HAYDEN, Boston Associate visiting surgeon, Massachusetts General Hospital

- 2 30 *Pitfalls of Chemotherapy and Antibiotics in Surgery* DR. ALLEN G. RICE, Springfield Consulting surgeon, Springfield Hospital
- 2 50 *Intellectual and Emotional Evaluation of the Sick Child* DR. JAMES MARVIN BATY, Belmont Professor of pediatrics, Tufts College Medical School, physician-in-chief, Boston Floating Hospital
DR. ROWLAND G. FREEMAN, Millis Assistant professor of psychiatry, Tufts College Medical School and psychiatrist, Boston Floating Hospital
- 3 15 *Diabetes — Some Fundamental Considerations* DR. W. RICHARD OHLER, Boston Chief, Diabetic Clinic, Boston City Hospital, president, New England Diabetic Association
- 3 40 *The Problem of Diagnosis and Management of Chronic Recurrent Headache* DR. H. HOUSTON MERRITT, professor of neurology, New York City Columbia University, College of Physicians and Surgeons; director of service of neurology, Neurological Institute, Presbyterian Hospital
- 4 05 *Mechanical and Clinical Considerations in the Medical Care of Patients with Low Back Pain* DR. WILLIAM B. SNOW, New York City Assistant professor of medicine, Columbia University, College of Physicians and Surgeons, director, Department of Physical and Occupational Therapy, Columbia Presbyterian Medical Center
- 4 30 *A Motion Picture Entitled "Fractures — An introduction"*

WEDNESDAY EVENING, MAY 25

- 6 00 Cocktail Party (CRYSTAL ROOM, HOTEL SHERATON)

Tickets must be procured in advance

- 7 00 Annual Dinner of the Massachusetts Medical Society (BALLROOM, HOTEL SHERATON)

Presiding

DR. DANIEL B. REARDON, president, Massachusetts Medical Society

Guest Speaker

ROSCOE POUND, LL.D., University Professor, Emeritus, Harvard University, formerly dean, Harvard Law School The Professions in the Society of Today

Ladies may be invited to attend the dinner

Tickets for the dinner must be procured in advance of the meeting

THURSDAY MORNING, MAY 26

Fifth General Session

LITTLE THEATER, WORCESTER MEMORIAL AUDITORIUM

DR. JAMES T. BROSNAW, Chairman

DR. NORMAN B. McWILLIAMS, Co-chairman

- 9 00 *A Motion Picture Entitled "Physiology of Normal Menstruation"*
- 9 25 *Some Problems in Interpretation and Management of Chondromatous Tumors in Bone* DR. GRANVILLE A. BENNETT, Chicago Professor and head of the Department of Pathology, University of Illinois College of Medicine
- 9 50 *Diagnostic Procedures in Virus Diseases* DR. F. SARGENT CHEEVER, Wellesley Assistant professor of bacteriology and immunology, Harvard Medical School

- 10 15 *Management of Abnormal Uterine Bleeding* DR. GEORGE VAN S. SMITH, Brookline William H. Baker Professor of Gynecology, Harvard Medical School, surgeon-in-chief, Free Hospital for Women, Brookline
- 10 40 *Fetal Loss as Influenced by the Administration of Diethylstilbestrol* DR. OLIVE WATKINS SMITH, Brookline Director, Fearing Research Laboratory, Free Hospital for Women, Brookline
- 11 05 *Skin Manifestations of Avitaminoses* DR. CHESTER N. FRAZIER, Boston Edward Wigglesworth Professor of Dermatology, Harvard Medical School, chief, Dermatological Service, Massachusetts General Hospital
- 11 30 *Present Concepts of Nutrition* DR. FREDRICK J. STARE, Newton Professor of nutrition, Harvard School of Public Health, associate in medicine, Peter Bent Brigham Hospital

THURSDAY NOON, MAY 26

Section Meetings and Luncheons

12 00 m — 2 00 p m

Section of Surgery

STAGE, WORCESTER MEMORIAL AUDITORIUM

DR. ROBERT E. GROSS, Boston, Chairman

DR. FRANKLIN G. BALCH, JR., Boston, Secretary

Some Studies in Gastric Secretion of Surgical Interest DR. FRANCIS D. MOORE, Boston Moseley Professor of Surgery, Harvard Medical School, surgeon-in-chief, Peter Bent Brigham Hospital

Section of Obstetrics and Gynecology

MALE CHORUS ROOM, WORCESTER MEMORIAL AUDITORIUM

DR. JAMES F. CONWAY, Brookline, Chairman

DR. DANIEL J. MCSWENEY, Boston and Milton, Vice-chairman

DR. DUNCAN E. REID, Boston, Secretary

Management of Dysfunctional Uterine Bleeding DR. GEORGE VAN S. SMITH, Brookline William H. Baker Professor of Gynecology, Harvard Medical School, surgeon-in-chief, Free Hospital for Women, Brookline

Section of Dermatology and Syphilology

FEMALE CHORUS ROOM, WORCESTER MEMORIAL AUDITORIUM

DR. FRANCIS P. MCCARTHY, Boston, Chairman

DR. ALFRED HOLLANDER, Springfield, Secretary

Quantitative Serologic Test for Syphilis DR. CHESTER N. FRAZIER, Boston Edward Wigglesworth Professor of Dermatology, Harvard Medical School, chief, Dermatological Service, Massachusetts General Hospital

Section of Anesthesiology

ASSEMBLY ROOM, WORCESTER MEMORIAL AUDITORIUM

DR. MORRIS J. NICHOLSON, Boston, Chairman

DR. JACOB FINE, Beverly, Secretary

A New Plan for Graduate Teaching of Anesthesiology DR. ROBERT D. DRIPPS, Philadelphia Professor of anesthesiology, University of Pennsylvania School of Medicine

Section of Physiology and Pathology

MUSICIANS' ROOM, WORCESTER MEMORIAL AUDITORIUM

DR. MONROE J. SCHLESINGER, Chairman

DR. DONALD A. NICKERSON, Secretary

Diagnosis of Certain Skeletal Disorders That Give Rise to Cystic Lesions in Roentgenograms DR. GRANVILLE A BENNETT, Chicago Professor and head of the Department of Pathology, University of Illinois College of Medicine

THURSDAY AFTERNOON, MAY 26

Sixth General Session

LITTLE THEATER, WORCESTER MEMORIAL AUDITORIUM

DR. GEORGE L. SCHADT, *Chairman*

DR. JOHN F. CASEY, *Co-chairman*

- 2 00 *Current Trends in the Care of Depleted Surgical Patients* DR. FRANCIS D. MOORE, Boston Moseley Professor of Surgery, Harvard Medical School, surgeon-in-chief, Peter Bent Brigham Hospital
- 2 25 *Pitfalls in Anesthesiology* DR. ROBERT D. DRIPPS, Philadelphia Professor of anesthesiology, University of Pennsylvania School of Medicine
- 2 50 *Indications for Total Hysterectomy* DR. BAYARD CARTER, Durham, North Carolina Professor of obstetrics and gynecology, Duke University School of Medicine
- 3 15 *Obstetric Problems in Rural Districts* DR. PENRY L. B. EBBETT, Houlton, Maine Chief of staff, Aroostook General Hospital
- 3 40 *The Management of Posterior Tuberculous Sinuses Permitting Early Spinal Fusion in Pott's Disease* DR. EDWARD W. BOONE, Rutland Surgical Service, Veterans Hospital, Rutland Drs. JOHN J. CINCOTTI, chief of surgical service, ARNOLD M. SELZBERG, JOHN B. KELLEY, consultant in orthopedics, Veterans Hospital, Rutland
- 4 05 *The Use of Psychotherapy in General Practice* DR. LEO ALEXANDER, Newton Instructor in psychiatry, Tufts College Medical School, director, Neurobiologic Unit, Division of Psychiatric Research, Boston State Hospital
- 4 30 *A Motion Picture Entitled "Cervicitis: Etiology, diagnosis and treatment"*

SCIENTIFIC EXHIBITS

BOOTH

- 79 — *THE USE OF TANTALUM GAUZE IN VARIOUS FORMS OF HERNIOPLASTY*
Sponsor Memorial Hospital, Worcester
Exhibitor Dr. George R. Dunlop
- 80 — *THE USE OF COTTON IN THE OPEN TECHNIC INTES-TINAL ANASTOMOSIS*
Sponsor Memorial Hospital, Worcester
Exhibitor Dr. Donald Hight
- 81 — *PANTOPAQUE MYELOGRAPHY IN THE DIAGNOSIS OF PROTRUDED INTERVERTEBRAL DISKS*
Sponsor Memorial Hospital, Worcester
Exhibitors Dr. William J. Elliott, Dr. James R. Lingley and Dr. John F. Sheehan
- 82 — *CHRONIC PNEUMONITIS — CHOLESTEROL TYPE*
Sponsors Massachusetts General Hospital, Boston, Memorial Hospital, Worcester
Exhibitors Dr. Laurence L. Robbins and Dr. Ronald C. Sniffen
- 83-84 — *TOXIC HAZARDS IN THE PLASTICS MANUFACTURING INDUSTRY*
Sponsor Plastics Division, Monsanto Chemical Company, Springfield
Exhibitor Dr. Lamson Blaney
- 85 — *GENERAL AND PLASTIC SURGERY OF THE EYE.*
Sponsor Fairlawn Hospital, Worcester
Exhibitor Dr. E. Porter Jewett, Jr.
- 86 — *ADEMYOSIS UTERI*
Sponsor Fairlawn Hospital, Worcester
Exhibitor Dr. Arthur C. Brassau
- 87 — *INDUSTRIAL MEDICINE, WORCESTER, MASSACHUSETTS*
Sponsors Industrial physicians of Worcester
Exhibitors Dr. Karl T. Benedict and co-operating industrial physicians
- 88 — *ORTHOPEDIC SURGERY IN CHILDREN*
Sponsor Worcester City Hospital
Exhibitor Dr. John W. O'Meara
- 89 — *DISEASES OF THE EYE*
Sponsor Worcester City Hospital
Exhibitor Dr. Elton Yasuna
- 90 — *GENERAL SURGERY*
Sponsor General Surgical Staff, Worcester City Hospital
Exhibitors Dr. Benjamin Andrews and staff
- 95 — *ENDOMETRIOSIS*
Sponsor The Fallon Clinic, Worcester
Exhibitors Dr. John J. Manning, Dr. William G. Moran, and Dr. Elizabeth Fletcher
- 96 — *DIAGNOSTIC DISCOLORATIONS OF THE ABDOMINAL WALL.*
Sponsor The Fallon Clinic, Worcester
Exhibitors Dr. James T. Brosnan, Dr. John Meyers, and Dr. John Fallon
- 97 — *FEVERS UNCOMMON IN GENERAL PRACTICE*
Sponsor St. Vincent Hospital, Worcester
Exhibitor Medical Section
- 98 — *Sponsor The Worcester Foundation for Experimental Biology*
Exhibitor The Worcester Foundation for Experimental Biology
- 99 — *HOSPITAL REHABILITATION*
Sponsor Cushing Veterans Administration Hospital, Framingham
Exhibitors Physical Medicine Rehabilitation Service, Dr. Fritz Friedland, Chief, Paul D. Faden, Executive Assistant.
- 100 — *RESEARCH IN EPILEPSY*
Sponsor National Veterans Epilepsy Center, Cushing Veterans Administration Hospital, Framingham
Exhibitors Dr. Jerome K. Merlis, Dr. G. Kennethsen, and Dr. C. Grossman
- 101 — *THE PROGRAM OF REHABILITATION OF THE TUBERCULOUS*
Sponsor The Rutland Training Center
Exhibitors Dr. Oscar Feinsilver and Leonard F. Janes, MEd
- 102 — *STREPTOMYCIN IN THE SURGERY OF TUBERCULOSIS*
Sponsor Veterans Administration Hospital, Rutland Heights
Exhibitors Dr. John J. Cincotti and Dr. Edward W. Boone
- 103 — *THE TREATMENT OF PULMONARY TUBERCULOSIS WITH STREPTOMYCIN*
Sponsor Veterans Administration Hospital, Rutland Heights
Exhibitors Dr. Stanton T. Allison and Dr. Ralph Volk

104-106 — USE OF TRANSMETATARSAL AMPUTATION IN DIABETIC GANGRENE.

Sponsor Worcester Hahnemann Hospital

Exhibitor Dr Elwood O Horne

1 HIP NAILING

2 MODIFIED HIBBS' LUMBO-SACRAL FUSION

3 SPLINTS FOR KELLER BUNIONECTOMY

Sponsor Worcester Hahnemann Hospital

Exhibitors Dr Ralph S Perkins, Dr Herman L Matern, and Dr Robert L Moore, Jr

ESSENTIALS OF A MODERN NURSERY

Sponsor Worcester Hahnemann Hospital

Exhibitor Dr Joel M Melick.

RETROPUBLIC PROSTATECTOMY

Sponsor Worcester Hahnemann Hospital

Exhibitors Dr Lester M Felton and Dr Harold M Constantian

MODIFIED SPINAL ANESTHESIA IN CESAREAN SECTION

Sponsor Worcester Hahnemann Hospital

Exhibitors Dr Anthony D Vamvas and Dr Constance B Kahriss

CORNER 1

PHYSIOLOGY OF SURGICAL ANESTHESIA

Sponsor Department of Anesthesia, St. Vincent Hospital.

Exhibitors Dr James C McCann and Dr William E Martin, Jr

CORNER 2

Massachusetts Blue Shield

Dr Charles G Hayden

CORRIDOR

CANCER OF THE THYROID

Sponsor The Lahey Clinic, Boston

Exhibitors Dr Frank H Lahey, Dr Hugh F Hare and Dr William A Neissner

CORRIDOR

Springfield Municipal Hospital

Sponsor The City of Springfield

STAGE

AN X-RAY FILM PROJECTOR.

Exhibitors Dr Raymond A Dillon, Doris D Dillon, and Dr William P Murphy, Jr

TECHNICAL EXHIBITORS

1949

	BOOTH NO
Abbott Laboratories	78
Alkaloid Company	55
Ames Company, Inc.	16
Atlantic X-Ray Company	70
Ayerst, McKenna & Harrison, Ltd	2
Baker Laboratories	29
Beech-Nut Packing Company, Inc	37
The Best Foods Inc	53
Bilhuber-Knoll Corporation	59
The Borden Company	15
Brewer & Company, Inc.	66 & 67

Brown & Connolly, Inc	72
Buffington's Inc	20
Burroughs Wellcome & Company, Inc	33
Cambridge Instrument Company	45
Camel Cigarettes	17 & 18
Carnation Company	74
Ciba Pharmaceutical Products, Inc	32
Coca-Cola Bottling Company of Worcester	93 & 94
Coreco Research Corporation	4
Crosbie-Macdonald	3
Davies, Rose & Company, Ltd	7
Denver Chemical Manufacturing Company, Inc	51
The Doho Chemical Corporation	75
Dr-Dee Service, Inc	50
Edin Electronics Company	28
Endo Products, Inc	11
C B Fleet Company	77
General Electric X-Ray Corporation	68
Gerber Products Company	24
J E Hanger, Inc	31
Hanovia Chemical & Manufacturing Company	49
Harper X-Ray Company	13
Harrower Laboratory, Inc	61
H J Heinz Company	43
Hoffmann-LaRoche, Inc	30
The Junket Brand Foods	46
Kelley-Koett Manufacturing Company	62 & 63
George Laben	26
Lederle Laboratories Division	5
Eli Lilly and Company	1
M & R Dietetic Laboratories, Inc	40
E F Mahady Company	8, 9 & 10
McIntosh Electric Corporation	76
McNeil Laboratories, Inc.	19
Mead Johnson & Company	36
Medical Clearing Bureau, Inc	57
Medical Protective Company	12
National Drug Company	35
Nestlé Company, Inc	34
Parke, Davis & Company	38
Pet Milk Sales Corporation	64 & 65
Philip Morris & Company, Ltd, Inc	73
Picker X-Ray Corporation	47 & 48
Rare Chemicals, Inc	60
L & B Reiner	22 & 23
Sandoz Chemical Works, Inc	21
Saratoga Springs Authority	69
Schenley Laboratories, Inc	14
Schering Corporation	71
G D Searle & Company	6
Sharp & Dohme, Inc	42
Smith, Kline and French Laboratories	54
Spencer, Inc	25
E R Squibb & Sons	56
Surgeons and Physicians Supply Company	91 & 92
Tailby-Nason Company	27
U S Vitamin Corporation	52
Vaponefrin Company	39
Varick Pharmacal Company, Inc.	44
White Laboratories, Inc	58
Winthrop-Stearns, Inc	41

MASSACHUSETTS MEDICO-LEGAL SOCIETY ANNUAL MEETING

WEDNESDAY AFTERNOON, MAY 25

ROOM ONE, WORCESTER MEMORIAL AUDITORIUM

2 30 p m

PROGRAM

BUSINESS MEETING Election of officers

WAR CRIMES AND THEIR MOTIVATION DR LEO ALEXANDER,
formerly special consultant to the Secretary of War
Refreshments

EXHIBITION OF WORKS OF ART

by members of the

MASSACHUSETTS PHYSICIANS' ART ASSOCIATION

ROOMS TWO AND THREE, WORCESTER MEMORIAL AUDITORIUM

Daily 9 00 a m - 5 00 p m

May 24, 25 and 26

ANNUAL GOLF TOURNAMENT

WORCESTER COUNTRY CLUB

WEDNESDAY AFTERNOON, MAY 25

1:00 p m

DR FRANKLYN P BOUSQUET, *Chairman*

390 Main Street

Worcester, Massachusetts

Luncheon may be obtained at the club

WOMAN'S AUXILIARY OF THE MASSACHUSETTS MEDICAL SOCIETY

The registration desk will be located on the stage of the Worcester Memorial Auditorium. Registration will be from 9 00 a m to 5 00 p m on both days of the meeting

TUESDAY MORNING, MAY 24

11 00 Annual Meeting

The meeting will be held in Dean Hall, Worcester Woman's Club, entrance on Salisbury Street (Buffet luncheon, at a charge of 95 cents, served at the club)

TUESDAY AFTERNOON, MAY 24

2 00 Visit to Worcester Historical Society, Art Museum and American Antiquarian Society

4 30 Tea at Worcester Medical Library (57 Cedar Street)

WEDNESDAY MORNING, MAY 25

10 30 Bus Tour Starting from Worcester Memorial Auditorium (Luncheon at the Publick House, charge for bus tour and luncheon, \$2 50)

NOTICES

NEW ENGLAND CENTER HOSPITAL (JOSEPH H PRATT DIAGNOSTIC HOSPITAL)

30 Bennet Street, Boston

Lecture Hall 9-10 a m

MEDICAL CONFERENCE PROGRAM

Friday, May 6 — The Importance of Hypothalamus to Adrenal Cortical Function Dr David M Hume

Wednesday, May 11 — Pediatric Clinicopathological Conference Drs James M Baty and H E MacMahon

Friday, May 13 — Experiences with Grafting Procedures in Vascular Surgery Dr Charles A Hufnagel

Tuesday, May 17 — Rheumatoid Spondylitis Dr Edward H Fischer

Friday, May 20 — Clinical Uses of Aureomycin Dr Harvey S Collins

Tuesday, May 24 — Recent Investigations in Virus Diseases Dr Lewis W Kane

Friday, May 27 — The Effect of Trimethadione (Tridione) and Other Drugs on the Major Convulsive Seizures Produced by Di-Isopropyl-Fluorophosphate (DFP) Dr Harold E Himwich

Tuesday, May 31 — Biological Antagonists Dr John J Finn

From 9 to 10 a m on Wednesday (except the second Wednesday), Thursday and Saturday mornings, clinics will be given by members of the hospital staff. Medical Rounds are conducted each weekday except Saturday by members of the hospital staff from 12 to 1 p m. On the second and fourth Fridays of the month, May 13 and 27, Therapeutic Conferences will be held with round-table discussion from 2 to 4 p m. Dr Robert P McCombs as moderator. On the second and fourth Fridays, May 13 and 27, Dr Merrill Sosman will conduct X-Ray Conferences from 4 to 6 p m.

On Saturday mornings from 9 to 10 a m Surgical Clinics are conducted by Dr C Stuart Welch.

All exercises are open to the medical profession

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The following program of the Boston City Hospital House Officers' Association will be presented in the Evening Lecture Series

May 10 Precancerous Skin Lesions Stephen Rothman, M D, professor of dermatology, University of Chicago, the School of Medicine.

This program will be held at 7 00 p m in the New Cheever Amphitheater of the Dowling Building, Boston City Hospital. All interested persons are invited to attend.

SOCIETY MEETINGS AND CONFERENCES

MAY 6-31 New England Center Hospital (Joseph H. Pratt Diagnostic Hospital) Medical Conference Program. Notice above.

MAY 7 New England Society of Anesthesiologists. Page 401 issue of March 10

MAY 9 New England Heart Association. Page 668 issue of April 21

MAY 10 Harvard Medical Society. Lower Out Patient Department Amphitheater Massachusetts General Hospital

MAY 10 Harvard Medical Society. Page 702 issue of April 23

MAY 10 New England Society of Anesthesiologists. Page 702 issue of April 28

MAY 10 Boston City Hospital House Officers' Association. Notice above

MAY 11 Harvard School of Public Health. Page 702 issue of April 25

MAY 11 South Boston Medical Society. Page 702 issue of April 28.

MAY 11 Massachusetts Society of Examining Physicians. Page 703 issue of April 28

MAY 11 Norfolk District Medical Society. Page 702 issue of April 28

MAY 12. Chemotherapy of Leukemia and Lymphosarcoma. Dr William Dameshek. Pentucket Association of Physicians. 8 30 p m. Haverhill

MAY 16-19 American Urological Association. Biltmore Hotel Los Angeles California

MAY 18-21 Association for Physical and Mental Rehabilitation. Page 401 issue of March 10

MAY 18-21 American Orthopaedic Association. Page 702 issue of April 28.

(Notices concluded on page xix)



FIGURE 1 *A Variant of Cullen's Sign, Consisting of Two Paraumbilical Ecchymoses, Symmetrically Located over Points at Which Vessels Often Perforate the Anterior Rectus Sheath, and Another, Fainter Ecchymosis in the Umbilicus Itself*

The photograph was taken eight hours after a sudden hemorrhage from ruptured tubal pregnancy

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Number 19

A VARIANT OF THE HOFSTATTER-CULLEN SIGN IN INTRA-ABDOMINAL HEMORRHAGE FROM ECTOPIC PREGNANCY*

With a Note on the Mechanism of Its Production

JOHN FALLON, M D,† AND JOHN J. MANNING, M D ‡

WORCESTER, MASSACHUSETTS

ORDINARILY one thinks of Cullen's sign — when it is thought of at all — as the blue navel of ectopic pregnancy. Actually, other diseases can produce the phenomenon, it often appears away from the umbilicus, other colors are as frequent as blue, and it was first described by Hofstätter.¹ Cullen's² classic description and Brödel's⁴ painting of his case, however, taught the world to look for the sign and English-speaking nations to call it Cullen's.

The sign can be caused by intra-abdominal hemorrhage from any source and is counterfeited by other nonbloody fluids. After ectopic pregnancy, the next most frequently reported cause is acute pancreatic necrosis, but upon meeting the phenomenon one should consider everything capable of producing colored intra-abdominal fluid, whether in the peritoneal cavity, retroperitoneally or in the abdominal wall.

The mark may be red, purple, blue, green, tan, yellow or many colors. In the 70 occurrences (in ectopic pregnancy) that we have been able to trace, the location was most often at the umbilicus, but hernial sacs and old surgical scars are frequent sites. In 2 of the collected cases and in the case described below, the discolorations appeared in still other areas. These 3 cases suggest a hypothesis for the mechanism of production of the sign.

Stabler's⁵ patient, at an undeterminable time after the hemorrhage, had a sharply defined, comma-shaped, dark-purple mark, about 20 by 7 mm in diameter, located 2 or 3 cm downward and to the left of the umbilicus, a second, circular blue mark 2 or 3 cm in diameter, in the midline a third of the distance from the umbilicus to the symphysis, and a third mark the color of a fresh bruise, 2 or 3 cm in diameter, and "shaped roughly like the ace of clubs,"

in the skin over the left external inguinal ring. Inspection of the underlying peritoneum showed no gross abnormality; incisions into the marks themselves demonstrated ecchymoses. Stabler found no blood in the peritoneal tissues at the (unspecified) site of his incision. The amount of intraperitoneal hemorrhage was small, 90 to 120 cc.

Neumann's⁶ patient, with a large but unmeasured amount of partly clotted blood in the peritoneal cavity, on the tenth day after her first symptom showed two nonumbilical ecchymoses. One was at the level, but a little to the left, of the umbilicus, and the other was 2 or 3 cm beneath it in the midline, both were irregularly outlined, each approximated 2 cm in diameter, one was green, and the other yellow-green.

In the third of the 3 erratic cases, the patient (F C 24617) had three separate ecchymoses: a small, irregular stain in the umbilicus and in one quadrant of the umbilical ring and two larger circular stains, 7 cm in diameter, symmetrically located on either side of the umbilicus with their medial borders 6 cm from the midline. The color approximated that of venous blood, and its hue was constant although the intensity varied. Lines of varying intensity formed arcs of concentric circles the common center of which was the umbilicus, a phenomenon that we cannot explain. The two larger spots were slightly raised, none of the three was tender.

A photograph (Fig 1) was taken eight hours after the first symptom, which, conveniently for fixing the time of hemorrhage from the ruptured tube, was an unheralded syncope. The time of appearance of the sign is fixed as between four hours (examination by the referring physician, a competent observer) and six hours after syncope (discovery at examination on admission). The amount of blood, widely distributed throughout the peritoneal cavity and partly clotted, was 400 cc (300 cc measured, and 100 cc estimated).

*Presented at the annual meeting of the New England Surgical Society, New Haven, Connecticut, October 2, 1948.

†From the surgical services of the Fallon Clinic and St. Vincent Hospital.

†Surgeon Fallon Clinic and St. Vincent Hospital.

‡Surgeon Fallon Clinic, assistant surgeon St. Vincent Hospital.

The patient was thirty-seven years old, of moderate height, weighed 138 lb and had a muscular abdominal wall with average panniculus. No hot-water bottle, electric pad, cupping or other mechanical, thermal or chemical agent that might conceivably have given rise to the ecchymoses had been used. Search of the abdominal wall from without and from within, showed no anomalies, hernias, unusual umbilical depression, apertures or thin spots. There were no adhesions. Because of the degree of shock, which was out of proportion to the moderate hemorrhage, the discolored areas were not explored.

Many theories have been suggested to explain the mechanism of the Hofstatter-Cullen sign. In a thin, translucent hernial sac, dark-colored intraperitoneal fluid can be seen through the wall; this has been demonstrated artificially by us, and clinically proved by Esau's⁷ case, in which, after removal of the abdominal blood, the color in an umbilical hernia disappeared whereas that of a surrounding ecchymosis persisted. Transvisibility, however, would explain only a few of the reported cases.

Other theories advanced do not coincide with appearances that the eye records — for example, dilatation of umbilical veins or engorgement of omental vessels showing through the skin. Ordinarily, it is assumed that the color is from pigmented material that has penetrated the abdominal wall after crossing the peritoneal barrier by following adhesions or lymphatics or by finding subvisible peritoneal apertures. After crossing the peritoneum, the pigment is transported to the subcutaneous tissues by lymphatics, so, at least, goes the assumption.

There is a basis for such an assumption: networks of subcutaneous and deeper lymphatics in the abdominal wall communicate at the umbilicus with a similar network just external to the peritoneum.^{8,9} The relation between the umbilical pathway and metastasis from breast cancer has long been accentuated. Intra-abdominal cancer may metastasize to the umbilicus, as pointed out by Warner¹⁰ and others.

But it is not ordinarily the function of lymphatics to pick up material, carry it a little way and then discharge it into surrounding tissues. Lymphatics carry their burden, through glands and ultimately the vascular tree, away and out of sight. Lymphatics should prevent the appearance of Cullen's sign.

Furthermore, the pigment of the sign does not follow the course of a lymphatic or group of lymphatics, as does the inflammation in lymphangitis. Contrarily, the color has the appearance of being deposited in a spot from which it spreads by direct extension. Thus in the case described above, the regular circles were at least 1 cm. in diameter smaller when seen at admission than two hours later, when the photograph was taken. Incidentally, on admission the color was a brighter, more nearly arterial

red, and the small ecchymosis in the umbilicus was absent or so faint as to escape notice.

The locations of the signs in reported cases — the umbilicus, spreading outward from the umbilicus, in hernias and scars and especially the pattern of the case described, with symmetrical circles over points where vessels commonly perforate the anterior rectus sheath — suggest that, once the causative fluid has passed the peritoneum in such amounts that lymphatics do not carry it away, its distribution may be guided by fascial planes and fascial apertures, as in hypodermoclysis or extravasation of urine. There are major fascial gaps (thinning might be a better word) at the umbilicus, midline and inguinal rings and in hernias and scars, there are minor ones where vessels perforate the rectus sheath. In Stabler's case a discoloration appeared over the external inguinal ring, and both Stabler's and Neumann's patients showed marks in the midline and over possible sites of perforating vessels.

How does material cross the peritoneal barrier? Lymphatics external to the peritoneum, whether in intra-abdominal adhesions or the normal peritoneal space, would not transport material across the peritoneum but would only pick it up after crossing, and it is our impression that lymphatics do not habitually perforate the peritoneum. Scraping of holes in the peritoneum by hard lumps of feces in the colon seems far-fetched, anomalous, subvisible peritoneal apertures are reminiscent of Galen's inter-ventricular pores. No new or special hypothesis is needed. Peritoneum is not the formaldehyde-hardened, watertight bulkhead of dissecting-room memories but a living, permeable membrane passing both fluid and particulate matter. The bulkhead concept, however, persists in the subconscious, as witnessed by the wide acceptance of endometriomas in the umbilicus or abdominal wall as an argument against the direct-implant theory of endometriosis. Yet the fluids and cells of all peritoneal exudates, to get into the peritoneal cavity from the extraperitoneal vessels whence they originate, somehow must transpass the peritoneum. Evidence of peritoneal crossing in the other direction is provided by the choking of omental lymphatics, which are extraperitoneal, by the contents of a perforated hemorrhagic cyst. Large amounts of intraperitoneal blood disappear in twenty-four hours or, if clotted, in a few days.¹¹ Graphite passes through the peritoneum¹², so can a fertilized ovum — to develop in the subcutaneous tissues of the abdominal wall.¹³

Why do not colored peritoneal fluids always discolor the abdominal wall? A possible explanation is the intraperitoneal distribution of the fluid and the relative surface areas of various parts of the peritoneum. Of the total peritoneal surface available for the transpassing of material, parietal peritoneum is only a small fraction, and the peritoneum of the anterior abdominal wall is but part of the fraction. Intestine, mesentery and omentum may hold some,

much or all of a given intraperitoneal fluid away from contact with this fraction of a fraction

SUMMARY

The Hofstätter-Cullen sign need not be blue, can appear elsewhere than at the umbilicus and is far from pathognomonic of extrauterine pregnancy. Probably, it can be caused by any condition producing colored intra-abdominal fluid.

A variant of the sign is reported consisting of symmetrical, red, circular stains at either side of the umbilicus, over points where vessels often perforate the rectus sheath.

The location of the stains in this and in 2 somewhat similar cases, as well as the more ordinary localizations over hernias, in scars and at the umbilicus, suggests that the pigments that usually produce the phenomenon may reach their destination by following ordinary fascial planes and openings rather than by depending upon exceptional lymphatic function or subvisible peritoneal apertures.

10 Institute Road

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THE EFFECT OF ORAL THERAPY WITH COBALTOUS CHLORIDE ON THE BLOOD OF PATIENTS SUFFERING WITH CHRONIC SUPPURATIVE INFECTION*

JOSEPH C ROBINSON, M D,† G WATSON JAMES, III, M D,‡ AND ROBERT M KARK, M R C P (Lond)§

CHICAGO, ILLINOIS

DURING a study of prolonged suppurative infection in 91 young men, we observed reticulocytosis, which was followed by increases in hematocrit and hemoglobin values, in the blood of patients being given cobaltous chloride by mouth.¹ These findings were not completely unexpected since it has long been known that cobalt is a hematopoietic agent effective in deficient² and healthy animals.³ Therapy with cobalt apparently stimulates red-cell production in children,⁴ as well as in adults,⁵ and also protects animals from developing anemia when sterile suppuration is induced experimentally.⁶

As far as we are aware cobalt has not been employed in this country in the treatment of patients ill with chronic sepsis. This report therefore presents observations on the blood of 9 patients suffering with prolonged suppurative infections who were

treated for two to eleven weeks by the daily oral administration of 20 to 60 mg of cobaltous chloride.

MATERIAL AND METHODS

Methods

Hemoglobin determinations were made by a photoelectric method⁷, hematocrit values, red-cell counts, white-cell counts, reticulocyte counts and differential white-cell counts were done according to methods described by Wintrobe.⁸ Plasma volume was determined by Gregersen's⁹ modification of the technic of Gibson and Evans,¹⁰ using the dye T-1824, plasma iron, after that of Kitzes et al,¹¹ and plasma copper by a modification of the method of Cartwright and his associates.¹²

Patients

Nine male patients were selected for study. Their average age was twenty-five years (the oldest was thirty-six and the youngest eighteen years of age). Three patients had been injured by automobiles, and 6 had been wounded by bullets or fragments from land mines. When first selected for this study patients had already spent an average of twenty-eight months in hospitals because of chronic osteo-

*From the Medical Nutrition Laboratory, an installation under the jurisdiction of The Surgeon General, Department of the Army and the Department of Medicine, University of Illinois College of Medicine.

The opinions expressed in this paper do not necessarily represent endorsement by any governmental agency.

†Captain, Medical Corps, U. S.

‡Assistant professor of medicine, Medical College of Virginia, formerly Captain, Medical Corps, U. S.

§Associate professor of medicine, University of Illinois College of Medicine, attending physician, Research and Educational Hospital, Chicago; assistant director, Medical Nutrition Laboratory.

myelitis or chronic soft-tissue suppuration. At the time of injury and thereafter all patients had received adequate therapy with blood and blood substitutes and, in addition, had been treated with sulfonamide derivatives (usually sulfadiazine), penicillin and streptomycin. Reconstructive surgical procedures had been carried out on numerous occasions in all patients.

When first observed by us all patients showed evidence of chronic sepsis as judged by drainage

of cobaltous chloride in tablet form taken orally each day after meals. Treatment was continued for eleven weeks in 4 cases, for four weeks in a second group of 4 patients, and for two weeks in 1 patient. During this time none of the patients received transfusions or therapy with other hematopoietic agents.

Two patients (Cases 3 and 4, Table 1), whose wounds were infected with penicillin-fast organisms, had previously been given injections of penicil-

TABLE 1 *Initial and Final Levels of Red-Cell Counts, Hemoglobin, Hematocrit and Total Circulating Hemoglobin in 9 Patients with Chronic Suppuration Treated with Cobaltous Chloride*

CASE No.	DURATION OF COBALT THERAPY	DOSEAGE OF COBALT	MEASUREMENT	RED-CELL COUNT	HEMOGLOBIN	HEMATOCRIT	TOTAL CIRCULATING HEMOGLOBIN
	wk	mg /day		$\times 10^6$	gm /100 cc	%	gm
1	11	20	Initial	4.35	13.8	44.8	610
			Final	5.75	16.0	52.0	850
2	11	20	Initial	4.82	14.5	43.8	640
			Final	6.58	15.7	51.0	860
3	11	20	Initial	4.90	13.3	44.2	660
			At 8 weeks	5.35	14.9	46.5	762
			Final	4.68	12.5	41.0	650
4	11	20	Initial	5.10	13.5	41.7	650
			Final	6.10	15.3	50.0	880
5	7	60	Initial	4.66	13.6	41.3	550
			Final	5.50	14.5	48.0	780
6	2	60	Initial	5.10	14.0	45.5	810
			Final	6.30	15.7	51.0	990
7	4	60	Initial	4.48	12.3	38.0	670
			Final	5.38	15.8	53.0	1100
8	4	60	Initial	4.69	14.8	45.2	670
			Final	5.52	16.2	52.0	950
9	4	60	Initial	3.42	11.0	30.8	470
			Final	5.19	13.5	41.0	670

of pus from wounds, pyuria, continued fever or radiographic evidence of bone sequestra. There was no clinical evidence of vitamin or protein deficiencies although all patients had lost weight. The red-cell sedimentation rate was increased, and in all cases cultures of organisms were obtained from

lin on numerous occasions without clinical effect, and were again treated with penicillin while taking cobalt. The penicillin was administered at a time when reticulocyte response had already been observed and, in our opinion, did not affect the course of the illness.

TABLE 2 *Effect of Oral Therapy with Cobaltous Chloride on the Blood of Patients with Chronic Suppurative Infection*

GROUP	RED CELL COUNT	HEMOGLOBIN	WHITE CELL COUNT	NEUTROPHILS	LYMPHOCYTES	BASOPHILS
	$\times 10^6$	gm /100 cc	$\times 10^3$	%	%	%
Bed ridden controls without infection (10 patients)*	5.5	15.7	8.1	60.5	33	0.5
Patients with infection before therapy (9 patients)	4.6	13.4	8.8	56.0	38	1.0
Patients with infection after therapy (9 patients)	5.7	15.1	9.3	55.0	39	0.5

*Reported in earlier study.¹

†Figures for 4 patients only.

sites of sepsis.¹ The organisms were identified and were usually found to be resistant to penicillin or streptomycin. In these patients plasma iron levels were low, and plasma copper levels were increased. Control measurements of blood volumes, hemoglobin levels, hematocrit values and cell counts were made on at least two occasions before therapy was instituted.

After the patients had been observed during the control period they were treated with 20 to 60 mg

RESULTS

Hematologic data on individual patients are given in Table 1 and Figure 1. Average data for the 9 patients during the control period and at the end of therapy with cobaltous chloride are recorded in Table 2 and are contrasted with average data obtained from 10 patients bed ridden with fractures or orthopedic abnormalities, who were free from infection during their illness.¹

Before treatment, red-cell counts, reticulocyte counts, hemoglobin concentrations, hematocrit levels and total circulating hemoglobin were constant and reduced below the levels found in the bedridden control subjects. The significant deviations

occurred during the first eight weeks of treatment with cobalt. An extensive sequestrectomy of the femur was performed during the ninth week of therapy, and, during the next two weeks while he was still taking cobalt, the total circulating

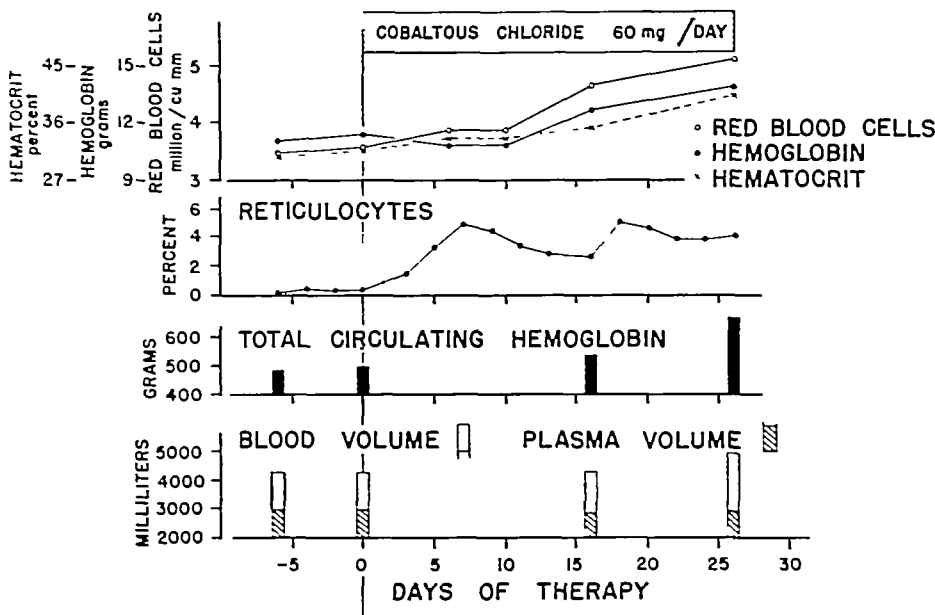


FIGURE 1 Effect of Therapy with Cobaltous Chloride on the Blood of a Nineteen-Year-Old Male Patient with Chronic Cystitis and Osteomyelitis Following a Bullet Wound

from the normal were in measurements of total circulating hemoglobin, which was reduced on the average 26 per cent below levels found in the controls

After treatment with cobaltous chloride reticulocyte responses were observed in each of the 9 pa-

tients hemoglobin, red-cell count and hematocrit levels returned to pretherapy levels

From Table 2 it can be seen that on the average the blood values of the 9 patients had reached normal levels after cobalt therapy. There was a significant change in the blood volume, owing in the

TABLE 2 (Continued)

EOSINO- PHILS	MONOCYTES	HEMATOCRIT	MEAN COR- PUSCULAR VOLUME	BLOOD VOLUME	PLASMA VOLUME	TOTAL CIR- CULATING HEMOGLOBIN	PLASMA IRON	PLASMA COPPER
%	%	%	cu microns	cc	cc	gm.	microgm./100 cc	microgm./100 cc
2.0	4.0	47.2	86	5060	2660	790	1.0	95
2.5	2.5	41.7	90	4550	2670	645	53†	144†
2.5	3.0	49.1	86	5470	2910	572	51†	156†

tients. These occurred as early as the fourth day and continued throughout therapy. The maximal reticulocyte percentages were usually observed between the sixth and tenth days, and did not exceed 5 per cent in any case. A typical reticulocyte response is shown in Figure 1. In this patient, as in the other 8 (Table 1), a steady increase in red-cell counts, hematocrit levels and total circulating hemoglobin followed the reticulocyte response. In Case 3 considerable increases in blood values oc-

curred during the first eight weeks of treatment with cobalt. The total circulating hemoglobin increased, on the average, 29 per cent above the levels before therapy. White-cell counts and differential cell counts showed few changes and mean corpuscular volume altered but slightly. In 4 patients, in whom measurements were made before and after treatment with cobalt plasma iron and copper levels were not affected by cobalt therapy.

myelitis or chronic soft-tissue suppuration At the time of injury and thereafter all patients had received adequate therapy with blood and blood substitutes and, in addition, had been treated with sulfonamide derivatives (usually sulfadiazine), penicillin and streptomycin Reconstructive surgical procedures had been carried out on numerous occasions in all patients

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	wk	mg /day		$\times 10^6$	gm /100 cc	%	gm
1	11	20	Initial	4 35	13 8	44 8	610
			Final	5 75	16 0	52 0	850
2	11	20	Initial	4 82	14 5	43 8	640
			Final	6 58	15 7	51 0	860
3	11	20	Initial	4 90	13 3	44 2	660
			At 8 weeks	5 35	14 9	46 5	762
			Final	4 68	12 5	41 0	650
4	11	20	Initial	5 10	13 5	41 7	650
			Final	6 10	15 3	50 0	880
5	7	60	Initial	4 66	13 6	41 3	550
			Final	5 50	14 5	48 0	780
6	2	60	Initial	5 10	14 0	45 5	810
			Final	6 30	15 7	51 0	990
7	4	60	Initial	4 48	12 3	38 0	670
			Final	5 38	15 8	53 0	1100
8	4	60	Initial	4 69	14 8	45 2	670
			Final	5 52	16 2	52 0	950
9	4	60	Initial	3 42	11 0	30 8	470
			Final	5 19	13 5	41 0	670

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lin on numerous occasions without clinical effect, and were again treated with penicillin while taking cobalt The penicillin was administered at a time when reticulocyte response had already been observed and, in our opinion, did not affect the course of the illness

TABLE 2 Effect of Oral Therapy with Cobaltous Chloride on the Blood of Patients with Chronic Suppurative Infection

GROUP	RED CELL COUNT	HEMOGLOBIN	WHITE CELL COUNT	NEUTROPHILS	LYMPHOCYTES	BASOPHILS
	$\times 10^6$	gm. /100 cc	$\times 10^3$	%	%	%
Bed ridden controls without infection (10 patients)*	5 5	15 7	8 1	60 5	33	0 5
Patients with infection before therapy (9 patients)	4 6	13 4	8 8	56 0	38	1 0
Patients with infection after therapy (9 patients)	5 7	15 1	9 3	55 0	39	0 5

*Reported in earlier study ¹
†Figures for 4 patients only

sites of sepsis ¹ The organisms were identified and were usually found to be resistant to penicillin or streptomycin In these patients plasma iron levels were low, and plasma copper levels were increased Control measurements of blood volumes, hemoglobin levels, hematocrit values and cell counts were made on at least two occasions before therapy was instituted

After the patients had been observed during the control period they were treated with 20 to 60 mg

RESULTS

Hematologic data on individual patients are given in Table 1 and Figure 1 Average data for the 9 patients during the control period and at the end of therapy with cobaltous chloride are recorded in Table 2 and are contrasted with average data obtained from 10 patients bed ridden with fractures or orthopedic abnormalities, who were free from infection during their illness ¹

fer from the blood to the bone marrow. There is good evidence in the literature that cobalt inhibits the respiration of micro-organisms as well as animal tissues and tumors¹⁵ and that it does so by inhibiting -SH groups of enzyme systems¹⁶. Oral therapy with sulfur-containing amino acids, such as cysteine and also to a lesser extent with histidine, inhibits the effects of cobalt in producing polycythemia in rats, and parenteral cobalt-cysteine complexes are also unable to produce polycythemia¹⁷. Ascorbic acid, a reducing substance, also inhibits the effects of cobalt in producing polycythemia in rabbits¹⁸ and dogs¹⁹.

As our patients developed a blue discoloration of the skin we speculated that the "cyanosis" and bone-marrow anoxia were due to methemoglobin, produced by cobalt interference with the normal reversion in the red blood cell of methemoglobin to hemoglobin — a reducing mechanism that is continuously taking place in the blood²⁰. We therefore examined the blood of 4 patients spectroscopically but were not able to detect methemoglobin after therapy with cobalt. The mechanism of cobalt activity in patients with chronic infection therefore remains unexplained and requires further study.

SUMMARY

Nine patients suffering with chronic suppurative infections were treated with 20 to 60 mg a day of cobaltous chloride given by mouth for a period of two to eleven weeks. In all patients a reticulocytosis was observed within six days. This was followed by increases in red-cell counts, in hemoglobin values, in hematocrit levels, in blood volume and in total circulating hemoglobin.

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Dr L. G. McLean and Mr T. Wallace of Smith, Kline and French Laboratories, arranged for the preparation of the cobaltous chloride tablets, and we wish to thank them for this service.

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Toxicity

During therapy with cobalt slight loss of appetite was observed in 2 patients. All patients developed a dusky discoloration of the skin, especially marked below the eyelids. This change in the color of the skin was probably due to the dye T-1824 used for measuring blood volumes, but it may have been an effect of cobalt therapy. No other abnormal signs or symptoms of cobalt toxicity were observed.

DISCUSSION

The anemia associated with chronic infection is usually not severe. With present-day attention to the protein and other nutritional requirements of the chronically ill and with present-day emphasis on the liberal use of blood and blood substitutes, gross anemia is rarely found in patients with prolonged sepsis. For example, only 6 out of 91 men suffering with chronic suppuration of the bones and soft tissues had hemoglobin concentrations below 12 gm per 100 cc. On the other hand, when blood-volume studies were done it was found that the total circulating hemoglobin was considerably reduced when compared with the total circulating hemoglobin of bed-ridden control subjects or when compared with the total circulating hemoglobin of healthy persons who were up and about.¹

The 9 patients reported in this paper were ill with chronic sepsis. In them plasma copper was elevated and plasma iron was reduced. Although hemoglobin concentrations and red-cell counts were reduced only slightly below levels found in the control subjects, the total circulating hemoglobin was reduced on the average by 26 per cent and may therefore have indicated lowered total blood volume.

Hematopoietic responses to therapy with cobaltous chloride, which were observed in each patient, indicate that cobaltous chloride produced an active stimulus to erythropoiesis, since a distinct reticulocytosis preceded the rise in erythrocyte count. Reticulocytes are not increased and do not increase spontaneously in patients at times when they are ill with chronic sepsis. The reticulocytes in the 91 patients mentioned above averaged 0.7 per hundred red blood cells and in only 1 case did they reach 2.0 per cent. Spontaneous increases in blood values were never observed when suppuration persisted. This, of course, is common knowledge.^{8, 12}

Preliminary observations on the effect of cobalt on the blood of normal and anemic persons have been reported in the German literature by Weissbecker and Maurer.⁶ They state that after daily oral therapy with 500 mg of cobalt chloride a reticulocyte peak occurred on the third day, and thereafter increases in erythrocyte, hemoglobin and hematocrit values occurred. Mean corpuscular volume and red-cell diameter decreased. The Price-Jones curve shifted to the left, and its base broadened. Osmotic resistance, serum bilirubin, white-

cell count and differential cell count remained unchanged. Blood volume increased, but plasma volume remained steady. In normal adults a "true" polycythemia developed, and blood levels returned to normal in patients anemic from blood loss.

In the anemia of chronic infection adequate responses occurred in some patients. However, in those who had severe chronic infection the effects of cobalt therapy were small and consisted of reticulocyte responses and bone-marrow maturation. The authors state that in patients with chronic infection the available serum iron was an index of ability to regenerate blood. In the 9 patients reported above, plasma iron was reduced but not to very low levels. These patients were well fed. Their nutritional status regarding protein and vitamins was good even after two years in the hospital. The German authors make no comment on the nutritional status of their patients ill with chronic sepsis, but it is reasonable to suspect that they were not so well fed as our patients. It is possible that nutritional disturbances in some patients account for failure to respond maximally to cobalt.

Weissbecker and Maurer used large doses of cobalt. They gave 500 mg by mouth each day and observed toxic symptoms in themselves and in their patients. These consisted of nausea, vomiting, diarrhea and reddening of the face and extremities, which was accompanied by hot flushes. With 60 mg a day by mouth after meals neither ourselves nor our patients experienced untoward symptoms. However, 2 of the patients suffered somewhat from anorexia.

The mode of action of cobalt on the blood remains a mystery. Specific effects of cobalt therapy on anemia are seen in cattle and sheep that graze on grass deficient in this trace element,² and good hematopoietic responses occur after therapy with very small amounts (0.1 mg) of cobalt. Castle,¹⁴ in a recent talk, suggested that cobalt-deficient animals are really suffering from vitamin B₁₂ deficiency. He speculated that normally bacteria in the rumen of cattle synthesize vitamin B₁₂—a cobalt-containing organic substance—and that the vitamin exerts a specific effect on hematopoiesis after it is absorbed. He also suggested that when the animals live on cobalt-deficient feed the intestinal flora are not able to form the vitamin. Consequently, the animals develop vitamin B₁₂ deficiency and become anemic.

It does not seem possible that cobalt exerts a specific effect on the blood in patients with chronic infections. Their anemia is refractory to therapy with liver, which contains vitamin B₁₂, and they require relatively large quantities of cobalt for erythropoiesis to take place. It is more likely that the hematopoiesis that follows massive cobalt therapy is due to a nonspecific stimulus to the bone marrow. This may be a consequence of generalized tissue anoxia or may follow impaired oxygen trans-

fer from the blood to the bone marrow. There is good evidence in the literature that cobalt inhibits the respiration of micro-organisms as well as animal tissues and tumors¹⁵ and that it does so by inhibiting -SH groups of enzyme systems¹⁶. Oral therapy with sulfur-containing amino acids, such as cysteine and also to a lesser extent with histidine, inhibits the effects of cobalt in producing polycythemia in rats, and parenteral cobalt-cysteine complexes are also unable to produce polycythemia¹⁷. Ascorbic acid, a reducing substance, also inhibits the effects of cobalt in producing polycythemia in rabbits¹⁸ and dogs¹⁹.

As our patients developed a blue discoloration of the skin we speculated that the "cyanosis" and bone-marrow anoxia were due to methemoglobin, produced by cobalt interference with the normal reconversion in the red blood cell of methemoglobin to hemoglobin — a reducing mechanism that is continuously taking place in the blood²⁰. We therefore examined the blood of 4 patients spectroscopically but were not able to detect methemoglobin after therapy with cobalt. The mechanism of cobalt activity in patients with chronic infection therefore remains unexplained and requires further study.

SUMMARY

Nine patients suffering with chronic suppurative infections were treated with 20 to 60 mg a day of cobaltous chloride given by mouth for a period of two to eleven weeks. In all patients a reticulocytosis was observed within six days. This was followed by increases in red-cell counts, in hemoglobin values, in hematocrit levels, in blood volume and in total circulating hemoglobin.

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ERYTHROPOIETIC EFFECT OF COBALT IN PATIENTS WITH OR WITHOUT ANEMIA*

LIONEL BERK, M D,† JOSEPH H BURCHENAL, M D,‡ AND WILLIAM B CASTLE, M D§

BOSTON AND NEW YORK CITY

COBALT in the form of one of its salts, usually cobaltous chloride or cobaltous nitrate, has been shown to produce polycythemia in amphibia, birds and mammals¹⁻³. In mammals the increased concentration of red blood cells in the circulation is due, as in other types of polycythemia, largely to an increase in the circulating red-cell mass⁴⁻⁶. That the polycythemia is produced by increased red-cell production is indicated by an initial or by a maintained reticulocytosis,⁶⁻⁷ and an increase in erythroid cells in the bone marrow⁸⁻⁹ and in extramedullary locations⁹. In some species the slight bilirubinemia⁷ presumably results from a partially compensatory increase in erythrocyte destruction. There is no evidence that cobalt administration causes the development of red blood cells containing an abnormal form of hemoglobin¹⁰ or one with a lessened capacity for the transport of oxygen.⁹ However, the resemblances of cobalt polycythemia to experimental polycythemia induced in various ways by anoxia of the bone-marrow cells may find an explanation in recent observations¹¹⁻¹² indicating that cobalt inhibits the respiration of certain bacteria, perhaps owing to the formation of partially reversible complexes between cysteine or histidine, cobalt and oxygen. Results in animal experiments suggest that such complexes are not readily dissociated in the body¹⁰ and so point to the possibility that their formation creates in effect anoxia of the erythroid cells of the bone marrow, with its characteristic increase in erythropoiesis.

Since the pioneer observations of the Waltners¹ in 1929, metallic cobalt or its salts have been administered in animals and in man in efforts to combat the anemia produced by disease. For example, Kleinberg, Gordon and Charipper⁸ reported that cobaltous nitrate was able to counteract the inhibitory effect on erythropoiesis of benzol administration in rabbits. Recently Wintrobe and his associates¹³ showed that cobalt administration abolished the anemia or even produced polycythemia in rats in which sterile inflammation had been created by the intramuscular injection of turpentine. Only a few results, for the most part all too

briefly documented, have been reported from the use of cobalt salts as a stimulus to erythropoiesis in human disease.¹⁴⁻¹⁸ However, almost at the time of the beginning of the present investigation, Weissbecker and Maurer¹⁹ briefly indicated in the German literature that the oral administration of 500 mg of cobaltous chloride daily produced with regularity in normal subjects reticulocyte responses and thereafter increases in red-cell, hemoglobin and hematocrit values. They confirmed the animal observations showing a decrease in mean corpuscular volume and diameter of the red blood cells and noted, likewise, an increase in circulating red-cell mass but not in plasma volume. No changes in serum bilirubin or in total or differential white-cell counts were observed. In some patients with the anemia of chronic infection, similar or less pronounced erythropoietic responses occurred. The toxic effects observed consisted of anorexia, nausea, vomiting, diarrhea and flushing of the face and extremities.

In the present work, an attempt was made to study the erythropoietic effect of cobalt first in hematologically normal patients. Then, especially because of the apparently successful results of Kleinberg and his associates⁸ in rabbits poisoned with benzol, it was proposed to extend the observations to patients with anemias refractory to recognized forms of treatment. If effective in causing increased erythropoiesis, cobalt therapy might be useful as a substitute, at least in part, for the repeated transfusions required in the treatment of such patients.

METHODS

Cobaltous chloride ($\text{CoCl}_2 \cdot 6 \text{H}_2\text{O}$) in the form of a 2.5 per cent aqueous solution was administered to 61 patients. Unless otherwise indicated, the dose of the solution employed was 4 cc containing 100 mg of cobaltous chloride given orally, thrice daily after meals, well diluted with water.

During a control period of not less than five days, two or more complete blood counts and daily reticulocyte counts were made. Then, with the institution of cobalt therapy, daily reticulocyte counts were continued for at least ten days in most patients, and complete blood counts were made at least once weekly for two to fourteen weeks. The red-cell and white-cell counts were made from venous blood samples in the usual manner with the use of United States Bureau of Standards certified pipettes. Hemoglobin estimations were done with an Evelyn photoelectric colorimeter with a factor of 2.58. It was considered that 15.6 gm of hemo-

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) Boston City Hospital, the Department of Medicine, Harvard Medical School, and the Memorial Hospital for Cancer and Allied Diseases, New York City.

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†Deceased formerly research fellow in medicine, Harvard Medical School, and research fellow, Thorndike Memorial Laboratory, Boston City Hospital.

‡Assistant attending physician, Memorial Hospital for Cancer and Allied Diseases, associate Sloan Kettering Institute for Cancer Research, New York City.

§Professor of medicine, Harvard Medical School, director, Second and Fourth Medical Services (Harvard) and director, Thorndike Memorial Laboratory, Boston City Hospital.

globin was equivalent to 100 per cent. Hematocrit determinations were performed by the method of Wintrobe, and the mean corpuscular volume and mean corpuscular hemoglobin concentration were calculated. Reticulocytes were counted by means of coverslips previously coated with a film of brilliant cresyl blue dissolved in absolute alcohol. After the film was dry, a fresh drop of blood was spread upon the coverslip in the usual manner and was thereafter fixed and counterstained with Wright's

into three groups chiefly on the basis of the amount of cobaltous chloride administered.

Subgroup A Eight patients with various psychoses were given 100 mg of the medication in a single daily dose for six days. During this period, as shown in Table 2, small reticulocyte responses were observed in 6 patients. The dose of cobalt was then increased to 200 mg, once daily. The 2 remaining patients then showed within seven days reticulocyte responses for the first time, and the

TABLE 1 *Types of Patients Treated and Number Showing Increased Erythropoiesis or Toxic Effects from the Oral Administration of Cobaltous Chloride*

DIAGNOSIS	TOTAL PATIENTS TREATED	PATIENTS TREATED FOUR WEEKS OR MORE	NO SHOWING ERYTHROPOIETIC EFFECTS		TOXIC EFFECTS	NO OF PATIENTS AFFECTED
			ON RETICULOCYTES	ON HEMOGLOBIN		
A. Patients without anemia						
Convalescents	17	10	17	10	Severe anorexia (1 patient) nausea and vomiting (1 patient) while on 1200 mg daily	2
Pernicious anemia in remission	12	0	—	—	Nausea and vomiting (12 patients) other symptoms described in text	12
Totals	29	10	17	10		14
B. Patients with anemia						
Chronic infections	5	4	2	2	Anorexia (2 patients) nausea and vomiting (2 patients) occasional vomiting (1 patient)	4
Refractory anemia	5	4	0	0	Nausea and vomiting (5 patients)	5
Leukemia and lymphoma	16	10	—	5	Anorexia (1 patient) nausea and vomiting (6 patients) occasional vomiting (4 patients) substernal pain (3 patients) dizziness (1 patient)	11
Chronic nephritis	2	0	0	—	Nausea and vomiting (2 patients)	2
Hypochromic anemia	2	0	1	1	Anorexia (2 patients)	2
Cooley's trait	1	1	1	1	Nausea and vomiting after 9 weeks (1 patient)	1
Hepatic cirrhosis	1	1	0	0	None	0
Totals	32	20	4	7		23
Grand totals	61	30	21	17		37

stain. The percentage of reticulocytes was then estimated by a count of at least 1000 red blood cells under the oil immersion lens.

RESULTS

The types of patients to whom cobaltous chloride was administered are indicated in Table 1. In the 31 patients who were treated for less than four weeks, cobalt administration was discontinued in 24, chiefly because of the irritant effects on the alimentary tract noted in Table 1, and in 7 convalescent subjects because early discharge from the hospital rendered further observations impossible. The erythropoietic effects observed in the patients without anemia are summarized in Table 2, and illustrations of those noted in 1 normal and in 3 anemic patients are presented in Figures 1 to 4.

Patients without Anemia

These 17 patients were without significant hematologic abnormality and can be subdivided

other 6 patients showed a second and slightly greater peak of reticulocytes. Thereafter, therapy with cobaltous chloride was continued with occasional unavoidable omissions, especially after the ninth week, for twelve weeks in all. During this time, moderate increases in red blood cells, in hemoglobin and in hematocrit of venous blood samples occurred in all but 1 case (Case 7, red blood cells), as shown in Table 2. No toxic effects were noted in any of the patients of this group, nor did any significant improvement in mental status develop.

Subgroup B Seven patients — in 4 cases convalescent from cerebral vascular accidents and in 1 each with prostatism, mental deficiency and senility — were given cobaltous chloride in a dose of 100 mg three times a day. In 6 patients the drug was administered for only one or two weeks prior to discharge from the hospital. However, daily counts showed within ten days reticulocyte peaks in most cases significantly greater than those in the cases included in Subgroup A. In the remaining patient

(Case 9), a sixty-seven-year-old man with marked generalized osteoporosis and osteoarthritis, the drug was administered for eleven weeks. The striking results upon red-cell and hemoglobin levels are of a pre-existing and otherwise silent duodenal ulcer, no unfavorable effects attributable to the medication were noted in the patients comprising this subgroup

TABLE 2 Erythropoietic Effects of Cobaltous Chloride Administration in Patients without Anemia

CASE No	RED CELL COUNT		HEMOGLOBIN		HEMATOCRIT		RETICULOCYTES					DURATION OF THERAPY
	INITIAL $\times 10^6$	FINAL $\times 10^6$	INITIAL %	FINAL %	INITIAL %	FINAL %	CONTROL %	PEAK 1		PEAK 2		
								%	day	%	day	wk
Subgroup A (100 mg daily for six days followed by 200 mg daily)												
1	4 14	4 58	71	83	35	41	0 8	2 8	5	3 7	15	12
2	4 74	6 26	89	105	43	52	0 4	2 1	7	3 1	14	12
3	4 65	5 63	85	108	41	51	0 6	—	—	1 4	14	12
4	4 75	5 70	90	100	43	49	0 8	1 9	6	2 2	12	12
5	4 36	5 23	83	106	40	49	0 8	1 2	4	3 1	12	12
6	4 03	4 88	80	93	37	43	0 8	1 5	4	2 5	15	12
7	5 29	5 18	87	109	43	47	0 8	—	—	2 2	14	12
8	4 63	6 99	88	103	41	51	0 4	2 0	5	2 8	13	12
Subgroup B (300 mg daily)												
9	3 92	6 93	81	116	38	59	0 9	3 0	6	—	—	11
10	4 70	4 67	92	91	47	43	0 7	4 1	10	—	—	2
11	5 01	5 41	85	92	41	44	1 4	5 3	7	—	—	2
12	4 04	3 82	75	66	37	36	0 8	6 1	6	—	—	2
13	4 25	—	81	—	37	—	2 2	5 1	4	—	—	2
14	4 37	—	80	—	43	—	1 9	8 3	6	—	—	1
15	4 71	4 95	91	92	45	45	0 9	2 3	9	—	—	2
Subgroup C (300 mg the first 600 mg the second 900 mg the third day and thereafter 1200 mg daily)												
16	4 41	5 30	83	98	42	52	0 5	1 6	7	—	—	6
17	4 41	4 88	87	96	42	49	0 8	1 6	6	—	—	7

summarized in Table 2 and are shown graphically in Figure 1. Although blood loss during the first week of treatment may have been responsible for the first reticulocyte peak, thereafter somewhat elevated reticulocyte counts appeared in successive waves of several days each. After ten weeks of treatment, the patient began to complain of poor appetite and sensations of fullness in the head. Consequently, cobalt administration was stopped a week later, and five days thereafter, at the height of the polycythemia, 500 cc of blood was removed

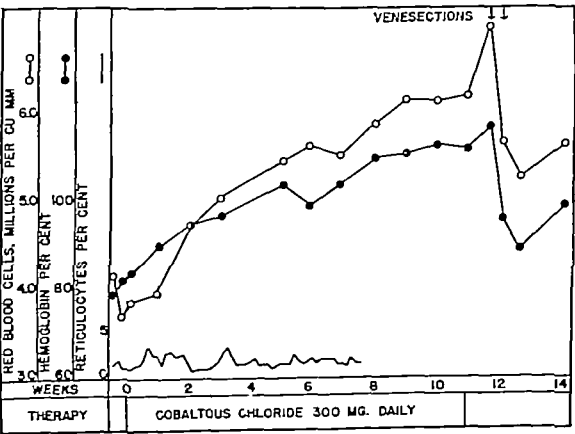


FIGURE 1 Results of Cobalt Administration in Case 9. This was a sixty-seven-year-old man with generalized osteoporosis and osteoarthritis. Because of manifest polycythemia after eleven weeks of cobalt therapy, two venesections of 500 cc each were performed. The red blood cells so obtained contained no abnormal forms of hemoglobin and survived normally in a suitable recipient.

on two successive days. Except for the hematemesis in this patient, which presumably, in the light of a subsequent x-ray examination, was due to irritation

Subgroup C. Two patients (Cases 16 and 17), who were convalescent from cerebral vascular accidents, received cobaltous chloride as follows: on the first day 100, on the second day 200, on the third day 300, and thereafter 400 mg three times daily. Both patients showed reticulocyte responses

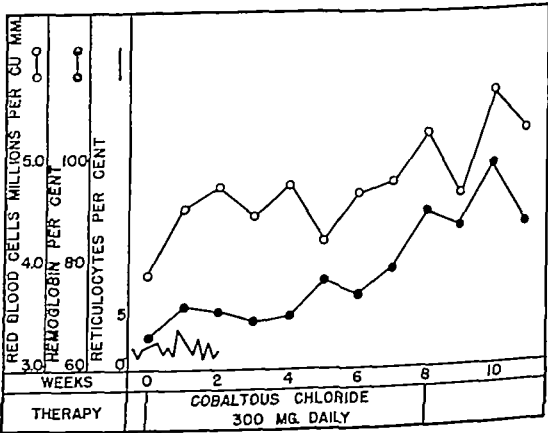


FIGURE 2 Results of Cobalt Therapy in a Fifty-Three-Year-Old Man (Case 18) with Mild Hypochromic Anemia due to Chronic, Moderately Active Rheumatoid Arthritis.

of slight degree. After two weeks of this regime, 1 patient (Case 17) demonstrated severe nausea and vomiting with hemoconcentration that disappeared when the drug was stopped. The other patient (Case 16) was successfully treated for six weeks. Daily reticulocyte counts were performed throughout this period and showed a wave-like rise and fall over periods of several days. During this time, the red blood cells, hemoglobin and hematocrit exhibited the moderate increase shown in Table 2.

The patient complained only of anorexia and had no nausea or vomiting.

An attempt was made to administer 100 mg of cobaltous chloride, three times a day, simultaneously to two groups of 6 patients with pernicious anemia maintained in complete remission in an outpatient clinic by means of monthly injections of concentrated liver extract. However, without exception each patient reported a week later that with the first dose of the medication symptoms appeared. Indeed, after either the first dose or the first few doses, nausea and vomiting, sometimes of considerable severity, compelled the discontinuation of the medication by the patient himself. Subsequent inquiry revealed that 2 patients had also noticed palpitation and 2 had experienced constipation (Table 1). In individual patients nosebleed, swelling of the hands and feet, abdominal pain, dizziness and diarrhea appeared clearly to result from the medication. All symptoms disappeared a few hours after the drug was stopped.

Patients with Anemia

Cobaltous chloride was administered at the rate of 100 mg, three times a day, to 32 patients with various types of anemia refractory to treatment. Of these, 20 took the medication for over four weeks. The number of each type of patient treated, as well as the untoward symptoms that occurred, is shown in Table 1. Of the 5 patients with moderate anemia associated with chronic infections (pulmonary tuberculosis in 3 and rheumatoid arthritis in 2), 4 re-

during the period of cobalt administration he ran a low-grade fever, and occasional sputums were positive for tubercle bacilli without evidence of change in x-ray films of the chest. Cobalt administration appeared to aggravate mildly this patient's occasional episodes of nausea and vomiting. The hematologic data for these patients are presented in Figures 2 and 3. Five patients with "refractory" anemia and hypercellular bone marrow, presumably of the type described by Bomford and Rhoads,²⁰ of

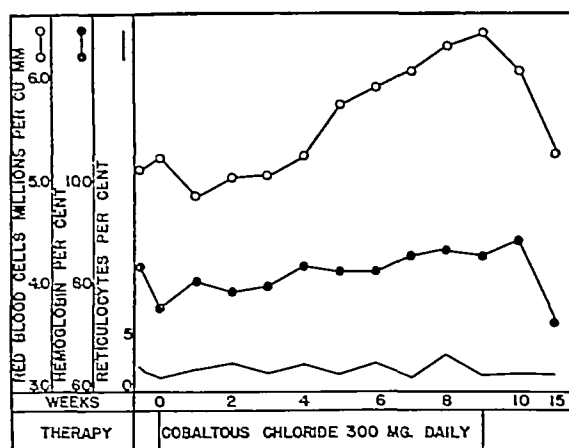


FIGURE 4 Results of Cobalt Therapy in a Thirty-Six-Year-Old Italian Woman (Case 22) with Familial Microcytic (Cooley's Trait) Anemia

Note the relatively greater increase in the red blood cells than in the hemoglobin in response to cobalt administration.

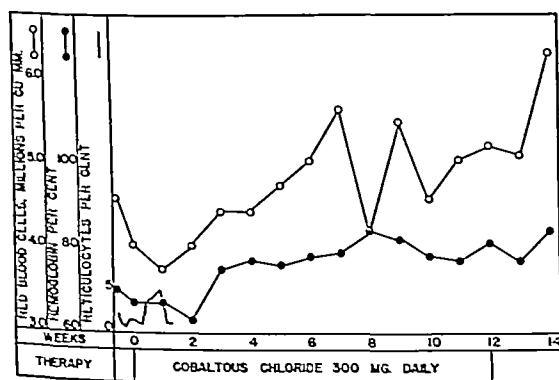


FIGURE 5 Results of Cobalt Therapy in a Forty-Eight-Year-Old Man (Case 19) with Mild Hypochromic Anemia due to Chronic, Advanced Pulmonary Tuberculosis

ceived treatment for over four weeks, of these, 2 patients (Cases 18 and 19) showed reticulocyte responses and subsequent rises in blood values. Case 18 was a fifty-three-year-old mason with chronic rheumatoid arthritis, who ran a temperature above 100°F and an elevated sedimentation rate during the period of cobalt administration. Case 19 was a forty-eight-year-old pipe fitter who showed multilobar cavitation of the upper right lung and nodular lesions in the centers of both lungs. On bed rest

whom 4 were treated for over four weeks with cobaltous chloride, yielded no definite reticulocyte responses or rises in blood values.

Sixteen patients with anemia accompanying various forms of leukemia or lymphoma were treated with cobaltous chloride. Of these, 10 received the material for over four weeks. In 2, daily reticulocyte counts were made during the first ten days of therapy and showed no evidence of significant increase. In 2 other patients, both with anemia associated with reticulum-cell sarcoma, there was perhaps suggestive evidence of an effect upon circulating red-cell values that became apparent more than a month after cobalt treatment had been begun. Thus, in 1 patient (Case 20) during a period of four months, nitrogen mustard therapy on three occasions and multiple transfusions within a few days of 2500 or more cc of whole blood on four occasions failed to elevate the hemoglobin more than temporarily above 54 per cent. However, after cobalt therapy for two months, a fifth series of transfusions comprising 2500 cc of whole blood raised the hemoglobin promptly from 32 to 83 per cent. Cobalt therapy was then continued for two more months, during which the hemoglobin values remained above 85 per cent. Two months after the cessation of cobalt therapy, the hemoglobin was 72 per cent. At this time, because of enlargement

of lymph nodes, a course of nitrogen mustard therapy was given. A month later the patient's hemoglobin was 57 per cent, and he was again started on therapy with cobaltous chloride. Two weeks thereafter, when his hemoglobin was 39 per cent, he was given multiple transfusions comprising 3500 cc of whole blood, which brought his hemoglobin up to 73 per cent. During the next six weeks, cobalt therapy was continued, and the hemoglobin increased to 99 per cent. At that time cobalt therapy was stopped temporarily because of an episode of precordial pain, which recurred a few days later when cobalt was again administered. For this reason, the medication was permanently discontinued. A month later the hemoglobin was still 83 per cent of normal. In the other patient (Case 21) the hemoglobin level prior to the institution of regular transfusions had gradually declined to approximately 50 per cent. Three months later the patient was placed on cobalt and began to receive small amounts of x-ray therapy. The transfusions were discontinued, and the hemoglobin remained above 80 per cent for over a year. In neither patient, unfortunately, were reticulocytes counted at the time of the initiation of the cobalt therapy. In each it is possible to ascribe the increase in red-cell and hemoglobin values either to the previous administration of a nitrogen mustard or to concomitant, though seemingly insufficient, irradiation therapy.

A third patient (Case 22), with chronic lymphatic leukemia, was given two courses of radioactive phosphorus one month and one week respectively before he was placed on 200 mg of cobaltous chloride daily. Cobalt administration was continued for five weeks, during which the elevated white-cell count fell gradually to normal and the hemoglobin increased from 39 to 58 per cent. The dose of cobalt was then reduced to 100 mg daily and was continued for another five weeks, when the hemoglobin had reached 94 per cent. Without further cobalt administration the hemoglobin slowly declined in the next eight months to 74 per cent, and the white-cell count gradually rose to about 80,000. Again, the interpretation of the dramatic hemoglobin response is complicated by the previous administration of radioactive phosphorus.

Two patients with the anemia of chronic nephritis could not tolerate the drug for more than a few days and exhibited no reticulocyte responses. Of 2 patients with hypochromic (iron-deficiency) anemia 1 showed a definite reticulocyte response and rise in red cells and hemoglobin despite the presence of inoperable carcinoma of the stomach. A clear-cut erythropoietic response to cobaltous chloride therapy was obtained in 1 patient (Case 23), a thirty-seven-year-old Italian housewife, with familial microcytic (Cooley's trait) anemia. The pertinent hematologic data are presented in Figure 4. Moderate nausea and vomiting appeared after nine weeks

of therapy and persisted for six days until the medication was discontinued. A patient with moderate anemia due to cirrhosis of the liver was given cobaltous chloride for more than four weeks without detectable effect on reticulocyte or other blood values.

DISCUSSION

On the basis of these observations, it seems clear that cobaltous chloride when administered in man in sufficient doses causes with some regularity increased erythropoiesis in hematologically normal subjects. The reticulocyte responses occurred within ten days of the institution of cobalt therapy, and so resemble in their chronology those resulting from hemorrhage, anoxia or iron or liver-extract administration under circumstances appropriate to each. This is seemingly consistent with the possibility, referred to above, that cobalt interferes with the transport of oxygen in the erythroid cells of the bone marrow because of its ability to form oxygen-binding complexes with certain amino acids such as cysteine and histidine. If so, the agent would be expected to be effective in elevating the hemoglobin level in patients with little or no anemia rather than in those with severe anemia, in whom a powerful anoxic stimulus to erythropoiesis presumably already exists.

Like Orten and Bucciero¹⁰ in their animal experiments, we were unable to demonstrate any abnormalities in the light-transmission curve of oxy-hemoglobin using the Beckman spectrophotometer. The pigment was derived from circulating red blood cells removed from a patient (Case 9), nearly all of which had presumably been formed during the previous eleven weeks of treatment with cobalt. As this patient's red blood cells, when transfused into another patient of compatible blood group, survived normally according to identification made by appropriate differential agglutinations, no evidence was obtained that red blood cells produced while the patient was receiving cobalt were defective as vehicles for oxygen transport.

The erythropoietic responses observed in 2 patients with chronic infection confirm the preliminary report of Weissbecker and Maurer¹⁹ and further substantiate the observations of Robinson, James and Kark.²¹ The observations of Waltner,¹¹ of Baxter¹⁸ and possibly of Kato¹⁶ suggest an effect of cobalt in "secondary," presumably hypochromic anemias in children due to iron deficiency with or without infection. In our experience also cobalt was efficient in raising the blood values of 1 of 2 patients with hypochromic anemia due, presumably, to blood loss from an inoperable cancer of the stomach. Iron, however, would be the therapeutic agent of choice in such a patient unless it was rendered ineffective because the cancer was exerting a "toxic" inhibition on erythropoiesis resembling that perhaps existing in chronic infection.¹³ The

definitive erythropoietic response in 1 patient with familial microcytic (Cooley's trait) anemia indicates a possible use for cobalt therapy in a condition that is completely refractory to iron and other substitution treatment.

Because it was the main objective of the study, it was disappointing to find that cobalt was completely ineffective in raising the hemoglobin level in 5 patients with "refractory" anemia of idiopathic origin associated with hypercellular bone marrow.²⁰ The coincidental use of other forms of treatment rendered the results merely suggestive in the 2 patients with anemia associated with reticulum-cell sarcoma and in 1 with chronic lymphatic leukemia. No certain benefit was remarked in any of the other patients with leukemia or lymphoma. In the anemias of chronic nephritis and cirrhosis, our studies, though negative, are perhaps too few to permit conclusions.

The toxicity of cobalt at dosage levels capable of causing polycythemia is difficult to estimate from reports in the literature. When administered orally, cobalt salts are largely excreted in the feces, and even the portion absorbed from the intestinal tract is mostly lost in the urine within a few days.^{22, 23} Thus, at the height of the polycythemia produced in rats, only 40 to 50 microgm of cobalt may be found in the entire body of the animal.²⁴ When cobalt salts are injected, elimination is largely in the urine and bile,^{23, 25} but as much as 5 per cent may be retained by the tissues ten days later.²² Presumably as a result of the poor absorption of the cobalt salts, the production of significant polycythemia in the adult rat requires the daily oral administration of about 40 mg per kilogram of body weight, in contrast to only 2.5 mg of cobaltous chloride daily by injection.²⁶

Early observations in animals showed that when given orally in sufficient dosage to dogs cobalt salts caused irritation of the intestine and death in convulsions. Ten milligrams killed a frog in half an hour, and 300 mg was fatal to a rabbit in three hours. In dogs 200 to 300 mg per kilogram of body weight caused vomiting, diarrhea and sometimes acute nephritis. With larger doses, dyspnea and a fall of blood pressure appear, and death may result from cardiac paralysis.²⁷ On the other hand until a certain daily oral dosage level is reached, which varies in different species and individuals, there may be no signs of toxicity and then only a poor appetite, which promptly improves with the discontinuance of the cobalt.²⁸ In the opinion of LeGoff,²⁹ who has studied the subject of cobalt toxicity both in animals and in man, cobalt is not more dangerous than iron, the immediate toxic actions of which it seems to imitate. The subcutaneous injection of 10 to 50 mg of cobaltous chloride in human subjects caused a sensation of heat in the face and a fall of blood pressure. To one patient LeGoff gave 90 mg daily orally for a

hundred days, and to another 122 subcutaneous injections of 25 mg each during a period of three years, without apparent harm.

The chief manifestations of toxicity from the oral administration of cobalt in our experience were, as reported by others, referable to the alimentary tract: anorexia, heartburn, nausea and vomiting. In many patients receiving 300 mg daily these symptoms were minimal or absent, but in some they were a very real obstacle to the administration of the therapeutic agent. The promptness and consistency with which each of 12 patients with pernicious anemia in complete remission experienced severe symptoms referable to the gastrointestinal tract suggest that the typical achlorhydria or rapid emptying time of the stomach was responsible and may occasionally condition similar undesirable side effects in other patients.

A patient with chronic lymphatic leukemia was given an intravenous injection of 50 mg of cobaltous chloride dissolved in 250 cc of sterile physiologic saline solution on sixteen occasions during a period of thirty-seven days. Whenever a given rate of infusion was exceeded, he experienced burning sensations and flushing of the face. However, if two hours was allowed to elapse for the entire injection, little difficulty was encountered. On one occasion when 75 mg of cobaltous chloride was given to this patient intravenously, an episode of nausea, vomiting and bone pain occurred. No pathologic changes appeared in the urine of this patient or of any of the other patients during the period of cobalt administration.

Two patients, 1 with reticulum-cell sarcoma and the other with giant-follicle lymphoma, after being under treatment continuously with cobalt for one and two months, respectively, complained of severe substernal pain, which they attributed to the drug. In the first patient (Case 20), who was sixty-five years of age, the pain disappeared when cobalt administration was stopped for a few days, only to return when the therapy was resumed. An electrocardiogram was normal at the time, but when autopsy was performed four months later, an old septal infarct was found. In the second patient, aged fifty-eight years, the electrocardiogram was consistent with myocardial infarction. It seems doubtful that the cobalt administration was responsible for the production of the infarct, but it is understandable that the drug could give rise to symptoms in patients who probably already possessed an insufficient blood supply to the myocardium, especially if the fundamental action of cobalt salts is to interfere with intracellular respiration.¹⁰

As with any therapeutic agent, the possibility of injury from cobalt must be balanced against the urgency of the need for the drug. No one questions the use in skilled hands of irradiation or of war gases in the treatment of leukemias or other neo-

plastic conditions. These agents are frequently effective and though dangerous are less so than the uncontrolled disease against which they are directed. With cobalt there is perhaps little evidence of toxicity, at least after oral administration, other than irritation of the alimentary tract. However, we have found that there is also little probability of benefit in severe types of anemia otherwise unamenable to therapy. In mild anemias associated with chronic infections, the benefit due to the slight increase in hemoglobin that can be confidently expected may well be offset by the loss of appetite due to the drug. For these reasons, the clinical use of cobalt should probably be confined to cases of anemia in which other methods of treatment are clearly of no value. Thus, there is no indication for the use of cobalt as an adjuvant to liver extract or iron therapy. Moreover, it is likely that by critical determination of the daily level of reticulocytes during a period no longer than a week, the probable usefulness of the drug during a more protracted exhibition in any given patient can be assessed.

SUMMARY

The daily oral administration of 300 mg of cobaltous chloride to 17 patients without anemia produced slight reticulocyte responses in all within a week. Of the 10 patients given the therapeutic agent for over four weeks, moderate increases in red blood cells, hemoglobin and hematocrit were observed in all but 1.

Similar doses of cobaltous chloride were given for more than four weeks to 20 patients with various types of anemia refractory to other forms of therapy. In 2 of 5 patients with moderate anemia associated with chronic infections, in 1 of 2 patients with hypochromic anemia associated with inoperable carcinoma of the stomach and in 1 patient with familial microcytic (Cooley's trait) anemia, definite reticulocyte responses and rises in red-cell, hemoglobin and hematocrit values were observed.

In only 3 of 10 patients in the lymphoma group — 2 with reticulum-cell sarcoma and 1 with chronic lymphatic leukemia — was even suggestive evidence of ability to maintain higher erythrocyte and hemoglobin levels obtained. In none of 5 patients with refractory anemia and hypercellular bone marrow was erythropoiesis detectably affected. In 1 patient with the anemia of cirrhosis of the liver no response was obtained in an adequate trial. In 2 patients with anemia associated with chronic renal failure, given the drug for only a few days, no evidence of a reticulocyte response was noted.

Red blood cells produced by a patient during eleven weeks of treatment with cobalt contained spectrophotometrically normal oxyhemoglobin and survived normally when transfused into another patient.

In some patients the usual dose employed, 100 mg of cobaltous chloride thrice daily, caused anorexia or mild symptoms referable to the alimentary tract. In a few cases these symptoms developed only after the medication had been administered for several weeks. However, the same amount of drug in each of 12 patients with pernicious anemia in maintained remission at once caused nausea and vomiting sufficiently severe to result in prompt abandonment of the medication. In another patient similar intolerance developed after two weeks when 400 mg had been given thrice daily. Two patients fifty-eight and sixty-five years of age experienced precordial pain while being given 100 mg of cobaltous chloride thrice daily and exhibited clinical evidence suggestive of myocardial infarction. All types of symptoms were relieved within a few hours by discontinuation of the medication.

The possibility that the erythropoietic action of the drug depends upon a fundamental alteration of tissue respiration indicates the need for further studies of chronic toxicity in animals and clearly suggests that cobalt salts should be used in man only in the treatment of anemias resistant to accepted forms of treatment and then with caution.

We are greatly indebted for the opportunity to study some of the patients to Dr. Walter E. Barton and his staff at the Boston State Hospital, Mattapan, Massachusetts, and likewise to Drs. Maurice B. Strauss and Charles R. Blackburn, of the Cushing Veterans Administration Hospital, Framingham, Massachusetts. Appreciation is also due Miss Phyllis Gordon for the performance of many of the blood examinations and to Miss Theo Wood for others, as well as for the preparation of the figures.

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METHODS OF INDUCTION IN PEDIATRIC ANESTHESIA*

ROBERT M. SMITH, M.D.†

BOSTON

IN INFANTS and children the technic of induction of anesthesia demands careful consideration, if optimal results are to be obtained.

The success of the induction depends upon several factors, one of the most important of which is the preoperative handling of the child. The first objective is the elimination of fear. Intelligent parents can help in this by instilling confidence in their children, and convincing them that the doctors and nurses are going to help them. Much of this reassurance can be given at home before departure for the hospital. The hospital routine should be planned to avoid frightening the child. He should be admitted to the hospital at least the day before operation. This allows time to recover from being separated from his parents, and to become accustomed to hospital personnel and procedures. It also provides opportunity for adequate, leisurely workup. After a quiet night's sleep the child goes to the operating floor in a far more receptive state of mind than one who has been hurried into the hospital on the morning of operation.

The anesthetist should visit the child at least once before the operation. Receptive children may be told and reassured about what will take place at the time of induction. This calls for careful interpretation, not falsification. Preoperative medication is selected carefully at this time. Preoperative sedation is essential for all children who are old enough to become emotionally disturbed. Gentleness and finesse can do much to gain the co-operation of the frightened child, but a far greater kindness is done the child if adequate medication is relied upon for the major part of the effect.^{1, 2} The dosage of preanesthetic drugs cannot be dictated arbitrarily, since many variable factors are concerned. Approximate dosages for healthy children are presented in Table 1. Children should arrive on

the operating floor calm and drowsy. Here they should await surgery in a quiet room and with an attendant. The sleeping patient should not be disturbed. The others may be watched or quietly amused. Every attempt should be made to prevent them from becoming upset at this time. Such preparation, when successfully carried out, greatly increases the chances for an easy induction.

The choice of the agent and technic of induction depends upon the individuality of the child. Al-

TABLE 1 Approximate Dosage of Preanesthetic Drugs

AGE OF PATIENTS	WEIGHT	ATROPINE	MORPHINE	NEMBUTAL
yr	lb	mg	mg	mg
Newborn	7	0.065	—	—
1	21	0.13	1.0	35
2-4	27-35	0.18	2.0	50
4-6	35-45	0.22	2.7	65
6-8	45-55	0.26	4.0	100
8-10	55-65	0.32	5.4	130
10-12	65-80	0.36	5.0	160

though all children are different, it is possible to make a rough classification into groups that have certain definite characteristics.

INFANTS UNDER ONE YEAR OF AGE

Small babies require relatively little psychology in their handling in the operating room. They are usually hungry, and though they may sense the strangeness of their surroundings, they certainly have no apprehension of the impending procedure. In young infants the metabolic rate is relatively low,³ whereas the threshold of pain is high. Consequently, sedative drugs are not indicated. Atropine is used to prevent excessive secretions and to block vagal reflexes. If the babies cry preoperatively, they may be picked up and comforted so that they will not become tired or emotionally disturbed. It has been found that an infant's stomach may become distended after a crying spell.

*Presented at a meeting of the Philadelphia State Society of Anesthesiology Philadelphia October 9 1948.
From the Department of Anesthesia, Children's Hospital.

†Instructor in anesthesia Harvard Medical School chief of anesthesia Children's Hospital.

Some anesthesiologists advocate the use of such technics as spinal anesthesia, or pentothal and curare on small babies. Although unusual circumstances occasionally indicate the use of one of these methods, their routine usage in the small infant seems, in my experience, to be uncalled for and even dangerous. The smaller and weaker the baby, the simpler should be the methods used. The respiratory reflexes should be depressed as little as possible, and normal function should be encouraged. The most readily controlled drugs should be chosen rather than those of a lasting effect.

Although ether may be used safely for induction of small infants, it is so irritating that it may cause prolonged struggling and breath holding. Ethyl chloride is less irritant and produces rapid induction, but its toxic effect on the heart renders it undesirable. Divinyl ether, or vinethene, although toxic if used over a long period, is a safe inducing agent. It is more potent than ethyl ether and is less irritating. It increases the respiratory exchange, and does not cause reflex spasms. It appears to be the agent of choice for the induction of healthy infants and young children.

At the time of induction, the infant's clothes are loosened so that he may breathe and move freely. Since young patients are frightened if their eyes are covered, this practice is not carried out until they are asleep. A baby Yankauer mask with only four layers of gauze is employed. Holding the mask down over the infant's chin, the operator drops the anesthetic slowly at first, so that this new odor is introduced gradually to the patient. The mask is brought slowly upward over the mouth and nose until full concentration of the agent is reached. There is then usually thirty seconds to a minute of resistance and crying, after which the infant falls into rapid, full, regular, respiration and exhibits increasing muscular relaxation. At this time it is important not to administer the vinethene too rapidly, for such a procedure may cause a characteristic clonic motion. The patient should be held in light anesthesia with vinethene as the ether is gradually introduced. After thirty to sixty seconds a sufficient concentration of ether will have been established, and the vinethene may be discontinued. Vinethene-ether inductions average three or four minutes for infants.

Induction is facilitated if the infant cries and moves his arms and legs, for these activities promote the respiratory exchange. These patients rarely show evidence of passing through an excitement stage, nor do they vomit during induction. Certain members of this younger group, however, will quite confound the anesthetist. Instead of crying and struggling, they lie still, limiting their breathing to a minimal exchange, and even after fifteen minutes under an ether mask, they may still be rigid and awake. Such infants can often be induced to move and cry if the anesthetist gently rubs their

faces, passively moves their arms and legs or lightly massages their ribs. The most difficult patient is the baby who refuses to breathe at all under the anesthetic mask—he simply holds his breath. In such a case cyanosis quickly appears, and it is dangerous to attempt to outlast such a resistant infant. If two or three attempts at induction with a volatile anesthetic are fruitless, one should choose a less irritating agent.

Cyclopropane is very useful for induction of anesthesia in this young age group.⁴ Infants breathe it readily and with little struggling or breath holding. For this reason it is the agent of choice in ill, premature and resistant infants. However, cyclopropane has several characteristics that preclude it from being the first choice in all cases. Respiratory depression may occur, or a marked respiratory spasm with its resultant retraction of the ribs. Once a patient has been induced with a volatile anesthetic, the succeeding anesthesia level is easily stabilized, but with cyclopropane this level is maintained with more difficulty. The explosive hazard of this agent and the management of special equipment for its closed system administration are factors that should influence the anesthetist to elect the simpler methods.

There is a specific type of case worthy of mention—the infant with pyloric stenosis. As the pylorus is obstructed, there is almost always a large residue in the stomach. Not only is induction especially difficult in such cases, but also the operative procedure is made dangerous, for regurgitation and aspiration of stomach contents are frequent. Induction will be much easier and operation safer, if a small tube is passed through the nose and the stomach emptied *before* anesthesia is started. This should be performed on all patients with distention and upon healthy children who are suspected of having eaten recently.

CHILDREN ONE TO THREE YEARS OLD

Children in this age group are relatively sturdy and have elevated metabolic rates. Morphine is indicated for its analgesic effect, as well as for the purpose of lowering the metabolic rate. Although young children will usually not have definite fears concerning an operation, they are easily frightened and hard to control. Barbiturates are tolerated well and may be used to help sedation of active young children prior to induction with inhalation agents. Nembutal may be given an hour and a half before operation, and morphine and atropine forty-five minutes preoperatively.

An earnest attempt should be made to gain the confidence of these children by preoperative attention on the ward and in the waiting room. For patients who appear moderately co-operative, vinethene offers the advantages of simplicity, speed and safety. There will usually be resistance to any method of induction. Needles cause the greatest

disturbance, and the small veins offer targets that are not easy to hit. In general, there is less resistance to the cloth mask and vinylene than to the more bulky closed-system apparatus needed for the less irritating agents. The administration of any agent should be gentle but, once begun, should progress actively. Any faltering or lapse on the way may cause spasm or retching and will result in a prolonged excitement stage and excessive secretions. It is especially important to maintain unobstructed respiratory exchange during this phase of anesthesia. The patient's chin must be supported at all times, and a suitable airway and suction used when indicated. However, since any prolonged removal of the anesthetic mask during induction may allow rapid lightening of anesthesia and further complicate the picture, suctioning and so forth must be performed as rapidly as possible.

Children in this group cannot be reasoned with effectively. If they become frightened they may struggle and scream so actively during induction that sobbing, jerky respiration will continue long after full anesthesia is established. For the child who appears excited and is resistant, rectal anesthesia is undoubtedly the most successful. There is not the pain of the needle, and there is no odor nor mask. A smooth, uncomplicated induction is almost certain. If morphine has not been administered, avertin in doses of 80 to 100 mg per kilogram of body weight will give excellent basal anesthesia with a minimum of respiratory depression.⁵ It should be emphasized that serious respiratory depression may follow the combined use of morphine and avertin. If a sedative has been given with only partial effect, pentothal by rectum can be used to similar advantage.⁶ A 0.6 per cent solution of pentothal is easily prepared by a mixture of 0.5 gm in 75 cc of water, 2 cc of this solution per pound of body weight will quiet an active child, and make induction rapid and easy.

Although rectal anesthesia may seem the technique of choice in most cases, there are definite drawbacks. Children who are to receive avertin should have no other preoperative sedation, therefore, their stay on the operating-floor waiting room is apt to be most upsetting to them, as well as to those nearby. Another point against avertin is that it is mildly irritating and frequently acts as a purgative. Pentothal does not have this quality, but, like other barbiturates, it is not consistent or predictable in sedative effect until large dosages are used.

If the child is receiving an intravenous infusion preoperatively, the anesthetist has an excellent opportunity to inject 2 or 3 cc of 2.5 per cent pentothal into the intravenous tubing, and thereby effect a most pleasant induction. Cyclopropane may be called upon for the same uses as in the youngest age group—namely, for quick, non-irritating induction when indicated by special circumstances.

CHILDREN THREE YEARS OF AGE AND OVER

In the group of healthy children three years of age and over, the preoperative preparation becomes especially important because fear, imagination and previous experiences, either of the patient or those told him by his ward mates, can cause havoc with the child's emotions. In addition to atropine and morphine in suitable dosage, a barbiturate should be given to all these patients who are to have inhalation induction. Comparatively large dosages of barbiturates are required for effective sedation, but these relatively large doses have proved remarkably safe and free from side effects.

This group offers a special challenge to the anesthetist, for it should be possible to put each patient to sleep without making him cry or struggle.⁷ If the child is successfully medicated this can be done readily and with a wide choice of agents. Co-operative older children (five to ten years or over) are easily and pleasantly induced with nitrous oxide and oxygen or cyclopropane and oxygen anesthesia.

Some of these patients are apprehensive even after suitable premedication, and these require the most careful treatment. Five minutes devoted to putting a child into a better state of mind is time well spent. Most children of the preschool and school ages can be reasoned with if the proper avenue of approach is discovered. Those who have specific fears are often easily quieted if the subject of their concern is known and discussed. Many are afraid of being hurt, or of being put to sleep with ether. Others are afraid because they do not know what is going to happen to them, and some know what is going to happen and dread it. After a short attempt at rational reassurance, the anesthetist should actively divert the child's attention from the business at hand. The child's interest is easily turned to pleasant, familiar subjects such as his pets or his favorite hobbies.

The patient should be in a quiet side room for the actual induction. The anesthetic apparatus should be shown to the child and he should handle it, smell it and play with it. If this can be fitted into a game it is more readily accepted by the child. The apparatus may be used as a telephone or it may be described as a dream machine—one valve for dreams about ice cream, one for chocolate cake and so forth. Orange, lemon or peppermint flavors may be added to the apparatus at the patient's choice. If the child still shuns the apparatus, he may be allowed to make his own selection between open or closed mask, or intravenous induction. Frequently the opportunity to decide for himself will change his whole outlook on the procedure. The anesthetist will make it much easier for himself if he can start a story or game that has a definite continuity to it, and carry it throughout the whole induction. A song or story will help with the smaller

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MEDICAL PROGRESS

ORAL SURGERY (Concluded)

KURT H. THOMAS, M.D. *

BROOKLINE, MASSACHUSETTS

THE SURGICAL CORRECTION OF JAW DEFORMITIES

In children many jaw deformities can be treated by means of orthodontic procedures. Later in life, or if the deformity is severe, surgical correction may give excellent cosmetic and occlusal results. The deformities referred to are mandibular protrusion (prognathism), mandibular retrusion (underdevelopment or micrognathia) and open incisor bite or apertognathia. These deformities are frequently of congenital origin, often inherited (Hapsburg jaw), or acquired through malunion of a fracture, underdevelopment as in early cases of ankylosis or overdevelopment due to such diseases as acromegaly or leontiasis ossea.

One of two sites may be selected for the operative correction, the ascending ramus and the body of the mandible. For prognathism and mandibular underdevelopment both operations have their champions. For correction of apertognathia, the operation in the ramus is not suitable because closing the occlusion would cause distraction of the osteotomized ramus, and the action of the elevator muscles would cause recurrence.

The operation performed in the ascending ramus is a bilateral osteotomy, whereas in the body of the mandible an ostectomy is used for setting the jaw back in protrusion or closing it in open bite. For advancing the jaw in retrusion, a sliding, Z-shaped osteotomy is recommended.¹³⁵ If the jaw is protruding without open bite, a parallelogram is excised, if an open bite is also present, a wedge-shaped or rhomboid-shaped piece of bone has to be removed to allow, through angulation, the closing together of the anterior teeth. Thoma¹³⁶ presents a diagram that shows how the size of this piece of bone may be geometrically determined.

The following authors have recommended osteotomy in the ascending ramus for repositioning of the jaw: Babcock,¹³⁷ Hensel,¹³⁸ Smith and Johnson,¹³⁹ Hook and Taylor,¹⁴⁰ Ivy,¹⁴¹ Traynham,¹⁴² Moose,¹⁴³ Lloyd,¹⁴⁴ Stetzer,¹⁴⁵ Peterson¹⁴⁶ and others. Those who prefer an ostectomy in the body of the mandible are New and Erich,¹⁴⁷ Cameron and Stetzer,¹⁴⁸ Dingman,¹⁴⁹ Kemper,¹⁵⁰ Thoma¹⁵¹ and others. Those who use both procedures are Kazanjian¹⁵² and Waldrom.¹⁵³

An excellent discussion of the advantages and disadvantages of each method was given by Dingman.¹⁵⁴ He wrote that correction of the deformity and repositioning of the teeth may be accomplished by either osteotomy or ostectomy.

Osteotomy is accomplished by a transverse division of the ramus of the mandible and shifting of the bone backward, or forward, where it is held in position during the course of healing. The procedure is simple to execute, avoids the possibility of injury to the inferior alveolar nerve and does not entail sacrifice of useful bone, nor does it damage the mandibular arch or teeth. The operation can be done without contamination from the oral cavity, by means of a Gigli saw, or by open operation with an incision below the inferior border of the mandible. The obvious disadvantages are that a parotid fistula may form. Injury to the facial nerve and serious hemorrhage from the internal maxillary artery may occur. There may be derangement of the muscles of mastication. The possibility of over-riding of the fragments, nonunion, malunion and open-bite deformities must also be considered very serious disadvantages. It is more difficult to adjust bite irregularities when this method is used.

Ostectomy has many advantages. The site of operation is extremely accessible, and the bone section can be removed without interference with the inferior alveolar nerve or its associated structures. The operation also does not interfere with the muscles of mastication, fragments can be repositioned more accurately and satisfactorily. A

*Emeritus professor of oral surgery and Charles A. Brackett Professor of Oral Pathology, Harvard University, lecturer in oral surgery, Graduate School of Medicine, University of Pennsylvania, member, Board of Consultation, Massachusetts General Hospital.

children, the older ones may be encouraged to count by threes or fives, or to do a similar task that requires real attention

Restraints should not be used. Instead, children should be encouraged to use their hands to help hold the mask by themselves, or to hold an assistant's hand, but for companionship rather than restraint. An apprehensive child is not a good subject for nitrous oxide, since the relatively slow onset of anesthesia is apt to allow time for him to become frightened. In such cases, the more rapid induction with cyclopropane is an advantage in spite of its slightly greater hazard.

If there is a vein that looks easy of entry, a single needle puncture will effect an easy induction with pentothal (3 to 5 cc in 25 per cent solution). It should be mentioned that although induction of sleep with pentothal is rapid and easy, respiration is depressed, whereas laryngeal reflexes remain active. If full surgical anesthesia is to be obtained later with ether, it is sometimes found that the initial use of pentothal results in slower induction than when other agents, such as nitrous oxide and vinethene, are used.

PATIENTS WITH COMPLICATIONS

Patients who have complicating illnesses or are in poor general condition require special attention. Premature infants should not be subjected to volatile anesthetics. Cyclopropane provides a more gentle induction and gives adequate relaxation. In patients with elevated temperatures anesthesia can be induced with pentothal, and the patients can be maintained on cyclopropane, again with the avoidance of volatile anesthetics. The anesthesia in children with cardiac disease, such as patent ductus arteriosus, coarctation of the aorta and mild rheumatic heart disease, who are not cyanotic or in decompensation, may be induced as that in normal children. Those with cyanotic heart disease or with decompensation provide just cause for considerable concern. Adequate medication is of importance, for as sedation becomes more effective, oxygen demands decrease and the work of the heart is reduced. A marked improvement in the color of the blood is often observed when anesthesia is induced in properly medicated patients, even without the addition of oxygen. Usually, however, when one is dealing with cardiac patients, it is wise to saturate the blood with oxygen before the induction is begun. Then, pentothal-ether or cyclopropane-ether sequences may be administered with minimal excitement and hypoxia, and have proved to be effective methods of induction.

ANESTHESIA FOR OUTPATIENT OPERATIONS

Strangely enough, the group that presents some of the most difficult problems, and perhaps the greatest possibility for tragedy, consists of healthy

children who come into the outpatient clinics for such minor ailments as a cut finger or a fractured wrist. These children may have eaten liberally shortly before admission, and, of course, they are badly upset, both by the accident and by the trip to the hospital with their equally unstrung parents.

The traditional treatment received by such children included their being pricked with a needle, then after a long, fearful wait, being pulled away from their parents and forced down on a table under an ether mask. The noise of the ensuing struggle could easily be heard, and usually was, by the parents in the waiting room. Under such conditions induction was accompanied by intense, prolonged excitement, and also too often by copious vomiting and possible aspiration. The relaxation for surgery was poor, and after the operation the recovery period might involve several hours more of nausea and vomiting.

Unfortunately, relatively few surgical procedures can be done humanely on children under local anesthesia alone. General anesthesia is necessary, but in outpatient surgical operations in children ether should be avoided, owing to the danger of aspiration of vomitus. Although cyclopropane may appear to some to be the agent of choice for such work, its explosive danger seems to contraindicate its routine use for minor surgical procedures. Treatment of patients entering the hospital for operation with a full stomach has long been a serious source of danger. Several courses of action are open. Passage of a stomach tube rarely results in removal of the larger, more dangerous pieces of food. Methods to make the child vomit preoperatively are often terrifying. Waiting a prescribed period for digestion of food is usually ineffective. Still another method is to induce anesthesia rapidly with cyclopropane and pass an endotracheal tube—rather a major anesthesia for a minor operation. I prefer to avoid the use of ether and cyclopropane in such cases. My method of choice is to use a combination of agents that effect an easy induction and maintenance of anesthesia without irritation of the vomiting reflexes. Induction can be accomplished very well with avertin. The parents should be allowed to stand by and witness the gentleness of the procedure. After the child is asleep he may be carried into the operating room. There, light nitrous oxide-oxygen, supplemented, if necessary, by block anesthesia, will be adequate for most such minor procedures. The patient will usually react at the end of operation and be ready for discharge in half an hour, having been subjected neither to discomfort nor to danger. Procedures requiring only momentary anesthesia may be done under vinethene alone. Longer operations on older children may be done under intravenous administration of pentothal with nitrous oxide, but for most outpatients the combination of

reported during the past ten years, a collective review on the subject having been published in 1938¹⁷⁹

Hyperplasia

A large number of the oral tumors are not true neoplasms but are hyperplasias that develop because of chronic irritation from ill fitting dentures and malhygiene

Benign Giant-Cell Tumor

This lesion occurs as the so-called giant-cell epulis, a peripheral tumor found on the alveolar process and as the more important central type. Central giant-cell tumors are not rare in the jaws. They occur less commonly in the maxilla^{180, 181} than in the mandible. In the latter, they are found most frequently in the symphysis,¹⁸¹ but may occur anywhere.¹⁸²

In children a frequent place of development is at the site of resorption of the deciduous teeth.¹⁸³ Conservative curettage is recommended,¹⁸⁴ followed by cauterization with phenol. A review of the literature has been made by Bernick.¹⁸⁵ The relation of these tumors to parathyroid activity is of interest. The statement is unwarranted that all benign giant-cell tumors are due to increased parathyroid activity,¹⁸⁵ but it is essential that there should be a careful investigation of the blood chemistry, and the skeleton should be investigated by x-ray examination. A giant-cell tumor that was caused by hyperparathyroidism and receded after excision of the parathyroid tumor was recently reported.¹⁸³

Fibroblastoma

Oral fibromas are quite common. They occur in any part of the mouth and are also seen as central tumors in the jaws. These are frequently ossifying fibromas. A case involving almost the entire subdental area of the mandible was reported in a woman forty-one years of age.¹⁸⁴ She complained of periodic pain but she did nothing about it until her cheek and lip had become numb and her teeth sore.

Fibrosarcoma

Fibrosarcoma is much less common. It occurs as a peripheral and as a central tumor. The malignancy varies somewhat. In a sixty-year-old man, a fibrosarcoma of the mandible, which was of moderate size but caused a pathologic fracture, recurred after resection of the jaw and caused lung metastasis.¹⁸⁶ A similar case,¹⁸⁷ which was of five years' duration and was entirely asymptomatic, was seen in a sixteen-year-old girl. The affected segment of the jaw was resected, and a bone graft was later inserted. There was no recurrence after two years. Not so fortunate was the outcome in a seventeen-year-old boy.¹⁸⁸ The tumor was of six years' duration and was treated by x-ray therapy. When it did not regress, the jaw with a mass extending from the canine to the molar region was excised. After

a year, it recurred locally, extending into the left cheek, nose, temporal region and frontal, sphenoid, and orbital bones. The patient died sixteen years after onset. A rare case of a fibrosarcoma arising from the capsule of the mandibular joint and causing excruciating pain for three years gave a great deal of difficulty in diagnosis. The patient was seen by many specialists. Disease of the ear and Costen's syndrome were thought of, but at an exploratory operation, a fibrosarcoma was found. It was removed by means of a condylectomy and after a year and a half there had been no recurrence.¹⁸³

Myxoma

Thoma and Goldman¹⁸⁹ report that this tumor has hitherto been regarded as similar to those in long bones, which tend to recur and are often malignant. A study based on 7 cases shows the jaw tumor to be benign, perhaps because it is of odontogenic origin. It is often associated with embedded¹⁹⁰ or with missing teeth and may have the x-ray appearance of a dentigerous cyst. It may be regarded as an odontogenic fibroma that has undergone myxomatous degeneration. The x-ray film generally shows a honeycomb appearance,¹⁸⁹ but the tumor may be cystic with an irregular, lobulated outline.¹⁸⁹ A large myxoma expanding the bone was reported in the symphysis mandibulae.¹⁹² The maxilla is also often involved¹⁸⁹, it may involve the entire half.¹⁹³ A very unusual myxoma was reported in the mandibular condyle.¹⁹⁴ It had been found in a forty-eight-year-old woman with Ménière's disease. For four years she had felt a swelling in front of the ear that had caused limitation of motion and pain. X-ray films showed a globular enlargement and trabeculation of the condyle, and after excision a diagnosis of fibromyxoma was made.

Neurofibroblastoma

Benign neurofibromas are peripheral or central tumors forming from the nerves that pass into the bones and supply the teeth. A neuroma has been reported as occurring on the palate of a fifty-five-year-old man.¹⁹⁵ It formed at the site of the larger palatine foramen. A neurofibroma forming a cystic defect, which in the x-ray film was seen to extend in the subapical area from the mental foramen to the ramus, was reported in a man aged thirty-three years.¹⁹⁶ It was diagnosed as a radicular cyst. It healed promptly and uneventfully. Another neurofibroma,¹⁹⁵ developing after a tooth extraction, encroached upon the maxillary sinus and invaded the zygomatic fossa. Martin¹⁹⁷ reported 2 cases. These were both cases of generalized neurofibromatosis with bulky invasion of the oral cavity. In 1 case, that of a three-year-old boy, the diagnosis was plexiform neurofibroma, which was slowly progressing and benign. In the second case, a girl five years old, the local tumor took on malignant, locally invasive characteristics and

dental splint, fitted to the mandible, often holds the fragments in place after very short periods of intermaxillary fixation. The only objections to the procedure are that it necessitates the sacrifice of one or two teeth on each side of the mandible, if an edentulous space does not already exist. It also necessitates the sacrifice of a section of mandibular bony structure. The fact that osteotomy offers almost uniformly successful results with a minimum of effort and only slight possibilities of complications indicates that this is the method of preference in most cases.

Osteotomy in the neck of the mandibular condyle was recommended by Schaefer¹⁵⁵. He performed the operation with a Gigli saw inserted through short skin incisions.

Another operation, called the "bow-back operation," was described by Pettit and Walrath¹⁶⁶. It was originated to correct unilateral prognathism, but can be used for bilateral cases as well. The authors perform an osteotomy in the surgical neck of the condyle that allows the jaw to be set back. The jaw is wired in this position for three weeks if fascia has been inserted between the fragments to form a false joint, or longer if bone union is desired. The advantage of this procedure is that it eliminates most of the objections raised against the other methods, but it seems to me not applicable to the correction of very extreme cases or to cases with open bite. For the correction of prognathism, a similar method was recommended by Smith and Johnson¹³⁹ and has since been perfected by Smith¹⁶⁷. In suitable cases he removes a parallel epipedonal section from the region of the sigmoid notch for transpositioning of the condyle.

CYSTS OF THE JAWS

Cysts of the jaws and mouth are generally classified according to their pathogenesis. The most important is the group of developmental cysts formed from odontogenic tissues and called odontogenic cysts. Other cysts occur from nonodontogenic tissue, they are caused by enclaved epithelium (fissural cysts^{158, 159}), or by epithelial remnants such as those found in the nasopalatine duct (incisive canal cysts^{160, 161}). In addition, there are extravasation cysts^{162, 163} of traumatic and non-traumatic hemorrhagic origin. Robinson¹⁶⁴ has recently presented a classification compiled after discussion and consultation with surgeons, radiologists and pathologists of note.

A large literature exists describing not only the various types of odontogenic cysts but also their anatomic distribution. They may be found in the tooth-bearing part of the mandible as well as the ascending ramus. In the maxilla they may encroach upon the nose or displace partly or completely the maxillary sinus. Cysts have often a hereditary history and then occur also in multiple form in the individual person.¹⁶⁵

The neoplastic potentialities of such cysts are important, the epithelial lining having been reported to give rise to adamantoblastoma forming mural thickenings first and invading the jaw widely later.^{166, 167} Cysts in which an epidermoid carcinoma developed were seen by Simmons¹⁶⁸ and Kent¹⁶⁹.

To facilitate roentgenologic diagnosis, aspiration of the cystic fluid and replacement with a radiopaque substance have been recommended as being especially useful for maxillary cysts.^{170, 171}

The treatment consists of complete enucleation of the cyst membrane, though there are some who prefer marsupialization or a modified Parnch operation.^{172, 174}

In these procedures the main part of the membrane is left in situ to protect the roots of involved normal teeth until, because of the evacuation of the cyst fluid, the cavity has become gradually eliminated. This method has the disadvantage of leaving behind pathologic tissue, perhaps with tumor or potentialities to form it, and, therefore, is not accepted as good practice by others. A new procedure combines the complete removal with the preservation of the involved teeth and, since it makes closure of the incision possible, eliminates prolonged post-operative treatments and irrigations to remove food from the recessed area. This procedure consists of space elimination by means of fibrin foam. It was recommended by Thoma¹⁷⁵ and utilized by him¹⁷⁶ and others¹⁷⁷ for filling the bone cavity after removal of the cyst sack with material that prevents the formation of a large blood clot, which would break down and permit healing by the formation of fibrous tissue and bone. The fibrin or gelfoam, soaked in a solution of thrombin and penicillin, is inserted, and the wound closed with closely placed, interrupted sutures. Both involved teeth in dentigerous cysts and adjacent teeth can be saved,¹⁷⁸ and if in a young person a partly formed tooth is accidentally removed with the cyst sac, it may be replanted with success,¹⁷⁶ since the pulp of such teeth with large apical foramina will become revascularized and will continue to develop and erupt.

TUMORS OF THE MOUTH AND JAWS

A great variety of tumors that occur in the mouth may be classified roughly as follows: tumors of the soft tissues of the oral cavity, peripheral tumors of the jaws, osteogenic tumors of the jaws, tumors of the jaws of odontogenic origin, and central tumors of the jaws of nonosteogenic and nonodontogenic origin. Like tumors in other regions, these growths may be benign or malignant, either with local invasive tendency or producing metastases.

To review what has been published on the diagnosis, pathology, treatment and aftercare of these tumors is beyond the scope of this article. The discussion is therefore limited to the more unusual cases

of tissue within the bone. If there is considerable calcification, the radiopacity may suggest an osteomatous growth.²¹⁵ On the other hand, if the replacement tissue has irregularly eroded and distended the cortex resulting in bony ridges on the internal surface, the x-ray picture may look monocystic¹⁹⁴ or multicystic or may resemble a central giant-cell tumor or adamantoblastoma. Schlumberger²¹⁵ concludes that ossifying fibroma is a variant of monocystic fibrous dysplasia. The lesion may involve one or both sides of the maxilla or may affect the mandible—in some cases all three. I believe that it is a tumor of medullary origin in which the tumor cells produce, by metaplasia, fibrous connective tissue in which osteoid is deposited irregularly in some²¹⁹ and as trabeculae in other cases.²¹⁵ The tumor is calcified partially in young and completely in older persons when it frequently ceases to grow. Furedi²²⁰ groups these lesions into hypostotic and hyperostotic.

Chondroma

This osteogenic tumor is rather rare. Jacobs²²¹ reported a cystic osteochondroma of the mandible that showed no recurrence three years after excision.

Osteogenic Sarcoma

Cases of both primary and metastatic types have been reported. The former includes a case that occurred in the maxilla²²² of a twelve-year-old girl and involved the antrum and occluded the nostril, and was treated by excision and x-ray irradiation. Another²²³ occurred in a forty-year-old woman, and grew slowly until it filled the entire vault of the palate. It was diagnosed as an osteogenic chondrosarcoma. A case²²⁴ that developed in the mandible was treated by resection of half the mandible. There was no evidence of recurrence a year later.

Of the metastatic cases, 1 was found in the maxilla, and 2 in the mandible. That in the maxilla²²⁵ occurred in a thirteen-year-old girl with a primary osteochondrosarcoma of the right tibia, which was treated by leg amputation, and a secondary tumor of the same type on the left femur, which was similarly treated. Six months later a swelling of the tuberosity of the maxilla appeared that was identical with that of the previously occurring tumors of the extremities.

The first of the mandibular metastases,²²⁶ which occurred in a twelve-year-old boy five months after a diagnosis of primary chondroblastic osteogenic sarcoma had been made, followed an injury (bruise) of the inner aspect of the tibia the month before. He was treated by irradiation. The metastasis occurred below the second molar. When the tooth was extracted the diagnosis was made from tissue attached to it. The other metastasis occurred in an eleven-year-old boy²²⁷ with osteogenic sarcoma of the tibia, which was treated by leg amputation.

Four months later a tumor formed in the third molar region invading the bone and pulp of a tooth.

Odontogenic Tumors

These tumors may be formed either from the epithelial component of the tooth-forming organ or from the mesenchymal part. In some cases—the mixed odontogenic tumors—both are involved. The following types are of interest.

Adamantoblastoma This lesion is considered a benign tumor that is locally invasive. A case with metastases to the lungs has been reported by Schweitzer and Barnfield.²²⁸ An adamantoblastoma was excised by removal of a section of the left mandible. Seven years later the tumor recurred in the ascending ramus and was treated with radium. It continued to grow, and involved the skull. Four years later, x-ray films revealed metastasis to each lung field. Two years later the patient died from local hemorrhages at the age of thirty-six years. An autopsy report was appended to the article.

Of the 16 cases reviewed for this article,²²⁹ 14 occurred in the mandible, and 2 in the maxilla. One of the latter formed a bulky enlargement of the lateral half of the alveolus of a seventy-two-year-old man. It extended to the maxillary sinus and nasal fossa. It was a polycystic tumor that could be completely excised. The other case¹⁶⁷ was that of a seventeen-year-old girl who on roentgenologic examination appeared to have a dentigerous cyst filling the antrum. When enucleated, the growth was found to contain epithelial elements that had formed coarse papillary projections and ill defined cysts.

The mandibular cases were either monocystic or polycystic. The monocystic tumors resembled either a follicular cyst^{196, 230} (without tooth) or a dense dentigerous cyst.^{167, 196} The polycystic tumors may form two or three large compartments or are definitely polycystic (soap-bubble effect).^{153, 196, 198} and may perforate.²³² Generally, the tumor forms in the molar region and invades the ramus,^{196, 229} but it may also occur in the anterior part of the mandible.²⁰⁰ Some of these tumors expand the bone to cause considerable asymmetry of the face,²³³ or an intra-oral mass,²²⁹ and in some cases a large swelling develops, as in that reported by Burford,¹⁹⁵ in which the chin was enlarged by a voluminous tumor the size of a grapefruit.

Recurrence after enucleation is common. Many of the patients were treated for excision of a "cyst," which later recurred as a polycystic tumor.^{153, 229, 232} That recurrence occurs even after resection, was brought out by the cases of Schweitzer²²⁸ and Dingman.²³⁴ Adamantoblastomas sometimes form in the dental follicle of an unerupted third molar,²³⁵ which, therefore, should be removed when the tooth is extracted. Treatment by enucleation is indicated in some cases. Penhale²³¹ shows excellent filling in with bone two years after operation. In polycystic cases, excision of a section or resection of the affected

resulted in death. Autopsy revealed no sign of general dissemination. An adrenal neuroblastoma in a two-year-old child was reported by Burford¹⁹⁸. Six weeks before examination, a small, nontender lymph node was found in the right submaxillary area. Bilateral orbital ecchymosis developed next, with considerable enlargement of the side and face and neck on the right. Extensive osteolytic and osteoblastic changes were found in the entire skeleton. Biopsy from the buccal mucosa disclosed an unclassified malignant tumor. The patient died eight days later. At autopsy, a neuroblastoma of the right adrenal gland was found, with widespread involvement of lymph nodes, bones and retro-orbital region.

Lipoma

This is an uncommon and perfectly benign tumor, which may form beneath the mucosa and produce a yellowish, soft tumor mass that is sometimes lobulated. More difficult to diagnose are lipomas occurring in the floor of the mouth beneath the sublingual gland, or in the infratemporal fossa. Here they may interfere with the motion of the ramus of the mandible. A case of this type was reported by Thoma¹⁹⁹.

Hemangioma and Lymphangioma

An intraoral nevus, occurring on the maxillary gingiva and of grayish-pink color, was reported by Field and Ackermann²⁰⁰. Burford et al.^{201, 202} state that cavernous hemangiomas of the oral cavity are relatively common. They are easily recognized by their grayish-blue color. Their report includes a large hemangioma of the lower lip in a thirty-two-year-old woman who was successfully treated with sodium morrhuate (5 per cent) injections. Another case reported from the same clinic²⁰¹ occurred on the upper lip in a nineteen-year-old Negress. This tumor was excised by ligation of two large vessels at the labiolingual fornix that entered the tumor mass. Thoma¹⁸³ described a hemangioma occurring in a fifty-nine-year-old woman and containing phleboliths that could be felt in the cheek and were demonstrable in x-ray examination. Erich²⁰³ reported a central hemangioma of the mandible, which caused intermittent stabbing pain and formed a cystic-appearing lesion that had the x-ray appearance of a giant-cell tumor. Lymphangioma usually occurs on the tongue and is frequently congenital, producing macroglossia,²⁰⁴ which, of course, is not a pathognomonic term. In a case reported by Rigg and Waldapfel²⁰⁵ the tumor occurred in two separate areas.

Hemangioendothelioma

This tumor was discussed by Cheyne and Silberstein,²⁰⁶ who, after reviewing the literature, reported 3 cases in an eight-year-old boy with a tumor on the lower lip, in a fifteen-year-old girl

with a growth on the roof of the mouth, and in a sixty-seven-year-old woman with a mass on the right side of the palate. All were studied pathologically. The authors state that clinically the tumor is generally an infiltrative growth, in some cases slowly growing and benign, whereas other hemangioendotheliomas, which are avascular, show greater metastasizing ability. The lesion is generally amenable to proper surgical removal.

Myoblastoma, Rhabdomyoma and Leiomyoma

These are rare tumors, occurring principally in the tongue. Myoblastomas, known as "rhabdomyoma granulocellulaire" in the French literature, are also found in the lip, soft palate, pharynx, uvula and jaws. Mann and Ash²⁰⁷ reported a case on the gingiva of both the maxilla and the mandible of a two-week-old infant. Thoma²⁰⁸ reported one excised from the tongue of a thirty-year-old woman. Considerable speculation exists regarding the etiology of myoblastomas. The controversy was discussed by Bernier,²⁰⁹ who, analyzing 17 cases,¹⁰ concluded that a number of tumors reported as myoblastomas on closer examination are rhabdomyosarcomas. Myoblastomas are small—seldom larger than 1.5 cm. in diameter.

A leiomyoma of the tongue occurring in a thirty-two-year-old Negro was surgically removed and was thought to be derived from the smooth muscle of the blood vessels. It appeared to invade the mandible at the angle.²⁰¹

Osteoma

Some osteomas, which are in reality bony hyperostoses, occur quite frequently on the palate, (torus palatinus) and the mandible (torus mandibularis).²¹¹ The head of the condyle occasionally becomes enlarged—a condition that has been variously reported as hyperplasia and osteoma of the condyle.^{212, 213} True osteomas occur peripherally on the oral²¹⁴ or cutaneous parts of the jaws,²¹⁵ and also as central tumors.¹⁸³ Sometimes multiple osteomas are found, generally in connection with similar formations in other parts of the skeleton.²¹⁶

Fibro-osteoma

This tumor is generally classified as an ossifying fibroma,¹⁹⁶ a term that is often used for a fibroma in which a certain amount of bone is produced but in which the bone plays an unimportant role, whereas "fibro-osteoma" is reserved for a tumor with typical clinical and histologic characteristics. This lesion has been called various names such as osteofibroma and fibrous osteoma, and some pathologists tend to consider it not as a neoplasm but as a bone dystrophy that gives rise to such names as localized osteodystrophia, localized osteitis fibrosa and fibrous dysplasia. Cahn²¹⁷ states that fibrous dysplasia is an expansive lesion with thinning of the cortex and no periosteal reaction. There is a replacement

lesions may destroy the bone around or adjacent to the roots of teeth simulating periodontal abscesses¹⁵³. In other cases ulceration¹⁵⁶ of the mucosa and the formation of fixed tissue masses on the gingiva and palate¹⁹⁷ are observed and are often of multiple occurrence^{257, 258}. Frequently, adenopathy is present²⁵⁸. The tumor varies in malignancy and may be a localized process or distributed throughout the lymphatic tissue²⁵⁴. Extensive destruction of the mandible and maxilla has been observed,²⁵⁷ and neurologic signs may be present, such as anesthesia of the lip²⁵⁸. A case of a girl three years old²⁰¹ illustrates the remarkable rapidity with which this tumor may grow, involving finally the entire left side of the face. Though these tumors generally respond well to roentgenotherapy, there was no response in the case described. A reticulum-cell sarcoma in a twenty-four-year-old man was reported by Goldman¹⁹⁶. After being treated for Vincent's stomatitis, it was biopsied and diagnosed. It was treated successfully by irradiation (7200 r). Salmon²⁵⁴ reported 2 cases that ended fatally.

Multiple myeloma A case of plasma-cell myeloma was diagnosed²⁰¹ by biopsy of a mass in the third molar region of an edentulous mandible. It was found to be part of a generalized process. Melov and Gunter²⁵⁹ reported another case of multiple myeloma, in which the largest and first lesion found produced pain and swelling in the mandible. On x-ray examination, a pathologic fracture of the mandible and multiple skeletal involvement were discovered.

Malignant melanoma Melanoma may occur in the mouth, since melanophores and dopa-positive cells are numerous in the oral mucosa, especially among the dark-skinned races, but this tumor is extremely rare. Brown and Byars²⁶⁰ give a good picture of a case occurring on the labial gingiva of a fifty-seven-year-old Negress. Arons²⁶¹ described a case occurring on the palate. Both patients died of metastases. Soderberg²⁶² reported 2 cases occurring in infants one month and two months old. Both were treated with radium, and both patients were free of disease five and six years later. A malignant melanoma of the floor of the mouth associated with an osteogenic sarcoma of the mandible was reported by Thoma²⁶³ in a twenty-four-year-old man. In spite of resection of the mandible and electrocoagulation of the wound, the patient died of a malignant giant-cell tumor seven months later.

Tumor of the retinal anlage This tumor, the first of its kind described, according to the reporter of the case,²⁶⁴ occurred in a six-month-old female infant, forming a firm mass, 5 cm in diameter, protruding from the palate and attached to the anterior part of the right maxilla. Though not malignant, it was radically removed and did not recur.

Metastatic carcinoma Metastasis is not uncommon. The jaws show in most cases radiolucent areas in the x-ray films except in carcinoma from the prostate,

which often causes osteoblastic activity. Adair and Herrmann²⁶⁵ reported 5 cases of cancer of the breast with metastases involving the mandible. Pain or anesthesia and loosening of teeth are early symptoms. Salmon and Darlington²⁵⁴ reported 4 cases, 3 occurring in the mandible causing swelling or pain, the fourth was a hypernephroma that formed on the hard palate two years after a nephrectomy. An embryonal type of metastatic carcinoma from the testicle causing pain and localized in the third molar region of the maxilla was found in a sixty-four-year-old man by Cameron and Stetzer²⁶⁶.

The case reports of some of the malignant tumors reviewed prove that many physicians and dentists continue to be responsible for unpardonable delay in the treatment of these lesions by trying various types of medication and thus postponing the early diagnosis that is essential. In other cases a great deal of harm is done by ineffective treatment or treatment that is too conservative. Malignant tumors should be treated only by those trained in tumor surgery who are familiar with the surgical anatomy of the region involved and are able to perform procedures radical enough to increase the chance of a cure.

CONCLUSION

Oral surgery is a broad field offering a great variety of interests. In this review surgical diseases only have been covered. There are many other conditions that the oral surgeon deals with, which some classify as oral medicine. These are either local lesions treated by nonsurgical means or symptoms of some systemic disorder such as avitaminoses, blood dyscrasias, dermatoses, neuroses or general organic and skeletal diseases, which often require for their elimination close co-operation with the physician or specialists in other fields.

1180 Beacon Street

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half of the mandible is recommended, followed by restoration of the jaw with a bone graft.^{182 232 233}

Cementoma This tumor is distinguished from odontoma by the fact that only one type of calcified tooth structure is formed. Cementomas occur more often in the mandible than in the maxilla. Bernier,²³⁶ investigating 15 cases, of which only 1 occurred in the upper jaw, found that their structure varied. Ten were trabeculated, and 5 were composed of cementicles. Many cases show multiple occurrence.²³⁷

Mixed tumor These are made up of epithelial and mesenchymal elements. Thoma and Goldman,^{238 239} in a review of 75 cases, distinguished three types: soft odontoma, soft and calcified, and completely calcified. The last is known as odontoma.

Odontoma is made up of masses of tooth tissue that has become calcified. It is considered a very benign tumor that ceases to grow after all soft tissue has been replaced. A case has been reported of a tumor that caused a gradual increase in size of the jaw, with alteration of the occlusion.²⁴⁰ Ordinarily these tumors are asymptomatic, even if large.²⁴¹ The excision is attended by the danger of fracture of the jaw. Therefore, in cases of extensive tumors, a two-stage operation is recommended by Callahan.²⁴²

The soft and partly calcified odontogenic tumors, on the other hand, may continue to grow. Both the epithelial components and the mesenchymal part have the ability of neoplastic proliferation. Thus the adamantoma-odontoma forms, in which, besides dentine and cementum, epithelial cells are present, both as differentiated cells (ameloblasts), which form enamel, and as undifferentiated adamantine epithelium, which is neoplastic and locally invasive.^{215 243} In other cases the mesenchymal part may take on malignant characteristics (fibrosarcoma), and form a so-called adamantino-sarcoma.²⁴⁴

Mixed tumor of salivary-gland type This tumor, also composed of epithelial and mesenchymal structures, is much more frequently malignant (adenocarcinoma) than the mixed odontogenic tumor. Being most common in the parotid and submaxillary gland, it occurs in the oral cavity. Ash²⁴⁵ reports the following distribution in 683 cases: parotid, 503, submaxillary, 55, sublingual, 2, lip, 40, palate, 80, and tongue, 3. The tumor also occurs in the mandible, forming what appears in the x-ray picture as a cystic lesion.^{197 246} It may invade the bone from an adjacent neoplasm.²⁰¹ An excellent collective review of the subject, with an analysis of 50 cases, has recently been presented by Cheyne et al.²⁴⁷ For differential diagnosis from inflammatory lesions, sialography has been recommended.²⁴⁸

Carcinoma

A long chapter could be written on the clinical appearance, complications and treatment of oral cancer, and many individual case reports and series

of cases in special regions of the mouth and jaws may be found in the literature. Epidermoid carcinoma is more common than the transitional-cell lesion and the adenocarcinoma, which is found in the palate, cheek and lip.²⁴⁹ Though the tumor is more common in the later part of life, no age is exempt. Two cases of malignant embryonal carcinoma have been reported—one in a child three years of age with a malignant epithelial tumor expanding the mandible and giving the appearance of an osteogenic sarcoma²⁵⁰, the other, in a nine-year-old child, probably was, like most of these tumors, formed from odontogenic epithelium in the jaw.²⁵¹

Epidermoid carcinoma varies greatly in its appearance, origin, clinical course, histologic structure and complications. It may form an ulcerating, papillomatous exophytic, fungating, indurated lesion often associated with leukoplakia, and careful inspection and palpation are necessary in the examination. Woodbury²⁵² gives examples of cases that are constantly observed in the outpatient clinic of the Massachusetts General Hospital because of persistent sores, swellings or lymph-node enlargement that the patient regards as being due to dental conditions. Secondary involvement of the mandible occurs for various reasons. Buirge,²⁵³ analyzing 71 cases, states that delay before diagnosis is made is the most frequent reason. Only 10 per cent of the patients were promptly referred by the dentist or physician to an appropriate source of therapy, in the other cases, there was an average delay of 8.4 months before definitive treatment was instituted.

More uncommon are other malignant tumors, which often give even the expert great difficulty in diagnosis. Fibrosarcoma and osteogenic sarcoma have already been discussed.

A Ewing tumor was reported as a possible primary lesion in a fifteen-year-old boy²⁰¹ complaining of a gradually increasing swelling of the body of the mandible, which responded dramatically to radiotherapy. In another case,²⁰¹ which showed striking radiologic changes in the mandible and involving the lateral wall of the left orbit and adjacent malar bone, a primary tumor involved the radius. Two cases were reported by Salman and Darlington.²⁵⁴ One, in a seventeen-year-old boy, caused a large swelling extending from the premolar area to and including the anterior border of the ramus of the jaw, after resection of the jaw, multiple bony metastases formed. The other occurred in a thirty-six-year-old woman who, after pregnancy, noticed numbness in the right mandible and pain. After a tooth extraction, which brought no relief, metastases occurred.

Lymphosarcoma

Stout²⁵⁵ discussed some of the reported cases and stated that 26 of 218 cases were primary in the mouth, pharynx or salivary glands. The gingival

lesions may destroy the bone around or adjacent to the roots of teeth simulating periodontal abscesses¹⁵³. In other cases ulceration²⁵⁶ of the mucosa and the formation of fixed tissue masses on the gingiva and palate¹⁹⁷ are observed and are often of multiple occurrence²⁵⁷⁻²⁵⁹. Frequently, adenopathy is present²⁵³. The tumor varies in malignancy and may be a localized process or distributed throughout the lymphatic tissue²⁵⁴. Extensive destruction of the mandible and maxilla has been observed,²⁵⁷ and neurologic signs may be present, such as anesthesia of the lip²⁵⁵. A case of a girl three years old²⁰¹ illustrates the remarkable rapidity with which this tumor may grow, involving finally the entire left side of the face. Though these tumors generally respond well to roentgenotherapy, there was no response in the case described. A reticulum-cell sarcoma in a twenty-four-year-old man was reported by Goldman¹⁹⁶. After being treated for Vincent's stomatitis, it was biopsied and diagnosed. It was treated successfully by irradiation (7200 r). Salmon²⁵⁴ reported 2 cases that ended fatally.

Multiple myeloma A case of plasma-cell myeloma was diagnosed²⁰¹ by biopsy of a mass in the third molar region of an edentulous mandible. It was found to be part of a generalized process. Melov and Gunter²⁵⁹ reported another case of multiple myeloma, in which the largest and first lesion found produced pain and swelling in the mandible. On x-ray examination, a pathologic fracture of the mandible and multiple skeletal involvement were discovered.

Malignant melanoma Melanoma may occur in the mouth, since melanophores and dopa-positive cells are numerous in the oral mucosa, especially among the dark-skinned races, but this tumor is extremely rare. Brown and Byars²⁶⁰ give a good picture of a case occurring on the labial gingiva of a fifty-seven-year-old Negress. Arons²⁶¹ described a case occurring on the palate. Both patients died of metastases. Soderberg²⁶² reported 2 cases occurring in infants one month and two months old. Both were treated with radium, and both patients were free of disease five and six years later. A malignant melanoma of the floor of the mouth associated with an osteogenic sarcoma of the mandible was reported by Thoma²⁶³ in a twenty-four-year-old man. In spite of resection of the mandible and electrocoagulation of the wound, the patient died of a malignant giant-cell tumor seven months later.

Tumor of the retinal anlage This tumor, the first of its kind described, according to the reporter of the case,²⁶⁴ occurred in a six-month-old female infant, forming a firm mass, 5 cm in diameter, protruding from the palate and attached to the anterior part of the right maxilla. Though not malignant it was radically removed and did not recur.

Metastatic carcinoma Metastasis is not uncommon. The jaws show in most cases radiolucent areas in the x-ray films except in carcinoma from the prostate,

which often causes osteoblastic activity. Adair and Herrmann²⁶⁵ reported 5 cases of cancer of the breast with metastases involving the mandible. Pain or anesthesia and loosening of teeth are early symptoms. Salmon and Darlington²⁵⁴ reported 4 cases, 3 occurring in the mandible causing swelling or pain, the fourth was a hypernephroma that formed on the hard palate two years after a nephrectomy. An embryonal type of metastatic carcinoma from the testicle causing pain and localized in the third molar region of the maxilla was found in a sixty-four-year-old man by Cameron and Stetzer.²⁶⁶

The case reports of some of the malignant tumors reviewed prove that many physicians and dentists continue to be responsible for unpardonable delay in the treatment of these lesions by trying various types of medication and thus postponing the early diagnosis that is essential. In other cases a great deal of harm is done by ineffective treatment or treatment that is too conservative. Malignant tumors should be treated only by those trained in tumor surgery who are familiar with the surgical anatomy of the region involved and are able to perform procedures radical enough to increase the chance of a cure.

CONCLUSION

Oral surgery is a broad field offering a great variety of interests. In this review surgical diseases only have been covered. There are many other conditions that the oral surgeon deals with, which some classify as oral medicine. These are either local lesions treated by nonsurgical means or symptoms of some systemic disorder such as avitaminoses, blood dyscrasias, dermatoses, neuroses or general organic and skeletal diseases, which often require for their elimination close co-operation with the physician or specialists in other fields.

1180 Beacon Street

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 35191

PRESENTATION OF CASE

A thirty-eight-year-old French-American fish-cutter was admitted to the hospital because of jaundice.

The patient was perfectly well until four months before admission, when he had an episode of vomiting food recently eaten. This was followed by the onset of flatulence and a sensation of upper abdominal fullness and anorexia, which persisted until the time of entry. There were occasional cramps and increased urge to defecate. Three months prior to admission the urine became darker. Two weeks later it was "reddish" for a period of three days,

this change was unassociated with pain, chills or fever. One week later jaundice and pruritus, associated with dark urine and clay-colored stools, developed. Two months before admission he noted the onset of a dull ache in the right upper quadrant, which became increasingly more severe, finally requiring an injection by his physician. Following this he was admitted to another hospital, where he remained for one month. During the first week in the hospital he was febrile, the temperature going as high as 102.5°F, but without chills or leukocytosis. Pain did not recur after the first hospital day, although jaundice persisted. Following a course of penicillin and aureomycin the temperature became normal, and the patient's appetite returned. A cephalin-flocculation test was negative. During the five weeks before entry he was on limited activity at home but despite a high-calorie, high-carbohydrate, high-protein, low-fat diet he became progressively worse. Jaundice persisted, flatulence, belching and "gas pains" became more severe, and it was noted that his weight, which before the onset of the illness had been 165 pounds, was now 130. During the week before admission he vomited just before each meal the food he had eaten at the previous meal. There was no history of hematemesis, although there were two questionable episodes of tarry stools three weeks before admission and on the day of admission, re-

spectively Although jaundice had been constant, the color of the stools varied greatly from dark brown to light tan to clay

Although his job was that of fish-cutter, he often supplemented his earnings by doing odd painting jobs and had been thus engaged, using a silver paint, shortly before the onset of the illness There was no past history of jaundice or other serious disease, and he used alcohol only moderately

Physical examination revealed a thin, jaundiced, middle-aged man lying comfortably in bed in no distress No spider angiomas were noted, and the chest and heart were normal The liver edge, on inspiration, was palpable 2 cm below the costal margin and was smooth and nontender No other organs or masses were felt, and there was no tenderness

The temperature was 100°F, the pulse 80, and the respirations 15 The blood pressure was 130 systolic, 90 diastolic

Examination of the blood showed a red-cell count of 4,900,000, with a hemoglobin of 15 gm, and a white-cell count of 8400, with 54 per cent neutrophils The total protein was 7.25 gm per 100 cc, with 5.02 gm of albumin and 2.23 gm of globulin (albumin-globulin ratio of 2.3) The cholesterol was 320 mg and the cholesterol esters 216 mg per 100 cc The van den Bergh test was 8.4 mg per 100 cc direct and 10.6 mg indirect The cephalin-flocculation test was negative in twenty-four and forty-eight hours, the thymol turbidity was 1.0 units, the prothrombin time 17 seconds (control, 15 seconds), and the alkaline phosphatase 9.3 units The urine gave a +++ test for bile on repeated examinations The stools varied in color from dark brown through yellow brown to metallic gray and, with a single exception, gave +++ or ++++ guaiac tests

In the hospital the patient seemed somewhat improved and ate extremely well, complaining that the diet given him was inadequate On the sixth hospital day the urinary urobilinogen was 3.7 Ehrlich units The serum amylase was 123 units and lipase 3.4 units per cubic centimeter The fasting blood sugar was 103 mg per 100 cc A plain film of the abdomen was negative for gallstones and showed no enlargement of the liver or spleen A roentgenogram of the chest was within normal limits A gastrointestinal series revealed no abnormality in the esophagus, stomach or duodenal cap There was slight narrowing of the duodenum in the post-bulbar region, but this was not constant The remainder of the duodenum showed no defect or displacement, and no stones were identified in the region of the common duct

On the tenth hospital day an operation was performed

DIFFERENTIAL DIAGNOSIS

DR EARLE M. CHAPMAN When one tries to reconstruct the story of jaundice the record says,

"the jaundice was constant" I cannot tell whether the jaundice was of three weeks' duration or longer I suppose it persisted throughout his illness

DR ALFRED KRANES The jaundice was constant but fluctuated in degree, not only clinically but also by chemical tests When the patient was discharged from the other hospital the icteric index was considerably below that of admission The jaundice never completely disappeared

DR CHAPMAN That is helpful The record states that the patient used alcohol only moderately Did you decide that it was moderate?

DR KRANES I did not know about that

DR CHAPMAN Was his temperature rectal or by mouth? I assume it was by mouth since it is not stated If so, he had a fever

DR KRANES He had no fever in this hospital except for one period of twenty-four hours

DR CHAPMAN I think we had better see the x-ray films at this point The record states that they were normal except for what is described as slight narrowing of the duodenum in the post-bulbar region

DR STANLEY M. WYMAN The films of the chest are not remarkable The liver shadow as described appears within the limits of normal There is no evidence of intrinsic disease in the stomach The narrowing of the post-bulbar region of the duodenum is seen at this point, and it appears on the spot films It does seem to change somewhat in caliber

DR CHAPMAN Compression from something external?

DR WYMAN Pressure from something extrinsic The mucosal pattern is perfectly normal in the entire area There is no evidence of convergence of folds It looks as if something is pressing on the distal portion of the duodenal cap, causing a narrowing rather than something intrinsic in the duodenum There is another finding of considerable value, and that is what I believe to be compression of the second portion of the duodenum on its medial aspect about at the junction of the middle and distal thirds over an area measuring 2.5 cm in length This is also seen on this spot film, in which there is a filling defect at this point It is not reproduced on all the films

DR CHAPMAN That lies in the region of the head of the pancreas anatomically

DR WYMAN Yes Although it is well visualized on only two or three films, and not on all films, the filling defect is a valid finding

DR CHAPMAN I think it is more significant than I was led to believe from reading the record There is more mischief in this area from looking at the film than I thought from the description What was found at operation is what they are asking me I will start by saying that I have no idea really It is a difficult diagnostic problem Since this man was a fish-cutter, we have to consider

Weil's disease It probably is a "red herring" Davidson* reported Weil's disease in fish-cutters in Scotland, who acquired it in their occupation This man did not have an acute disease and was almost afebrile, so I think we can exclude Weil's disease However, the illness started with dark urine

DR KRANES The dark urine noted the week before the jaundice was hematuria It had a good many red cells in it

DR CHAPMAN That is interesting The record said 'dark' urine, it did not say "bloody" urine

DR KRANES I did not see it His family said that microscopically it was full of red cells

DR CHAPMAN I thought of the possibility of Weil's disease The patient was a fish-cutter, and we have seen the disease among people with that occupation in Boston Yet this seemed like a chronic disease If it was a complication of Weil's disease we ought to find something like abscess in the region of the head of the pancreas This bothered me a little, but I decided to exclude it because the progress of the illness did not seem to fit the diagnosis and someone should have made a diagnosis of Weil's disease But there it is—he was a fish-cutter, with a febrile illness to start with Why did it take so long? I did not think of it last night when I first read the record, but now that I have seen the films I am thinking of the possibility of abscess I have to change my thinking of 11 30 last night

The laboratory evidence is confusing, but from it one gathers that there is no good evidence on which to base the diagnosis of intrinsic liver disease I do not see how we can support cirrhosis or infectious hepatitis All the laboratory changes are consistent with the intermittent type of obstruction to the outflow of bile The clinical description Dr Kranes gave us and the laboratory changes all fit together

We are faced with the question of what would lead to an intermittent obstruction in the region of the head of the pancreas What lesion would fit with the x-ray evidence? Of course the commonest thing in this location, even though thirty-eight years of age is a little young, is carcinoma of the head of the pancreas We know that carcinoma in the head of the pancreas can erode the ampulla of Vater and lead to blood in the stools and it can lead to intermittent obstruction and cause the type of distortion seen in the x-ray film That is the likeliest possibility, but there is one thing strikingly against the diagnosis of cancer I cannot believe that a man who had cancer and who died of it, let us say, would complain that the diet in the hospital was inadequate and want more food That is a clinical fact against carcinoma of the head of the pancreas That is the one state-

ment that I underlined as being against that diagnosis

Could he have had a stone, a so-called silent stone, in the head of the pancreas? A large non-opaque stone does not cause a shadow and could have bored in there and got mixed in with the pancreatic duct and eroded the whole area and caused mischief

If we go back to the beginning of the history, he had occasional cramps and increased urge to defecate when the illness started If we try to reconstruct the events from the beginning of the illness we have to consider silent stone in the head of the pancreas, not reflected here in the x-ray films, and then consider inflammatory reaction around it There must have been considerable inflammatory reaction around this area whatever it is, because the serum amylase was high (123 units), which is evidence of destruction of the pancreas The upper limit of normal is 40 units I might say in passing that jaundice has been described as coming on after penicillin and also described after pentothal anesthesia He did not have any such things injected into him, did he, Dr Kranes?

DR KRANES Penicillin was given by the family physician after the patient had become jaundiced because he was running a septic fever

DR CHAPMAN But he had had no operative procedure, before the onset of the illness I wondered if it might be related to an infected syringe or anything of that sort There was nothing of that nature antecedent that you know of?

DR KRANES No

DR CHAPMAN Was this, then, a stone, a tumor or an inflammatory mass? I am beginning to change my mind Last night I was all for cancer of the head of the pancreas or ampulla of Vater Having seen the films and reconstructed the story, however, I am now thinking that this mass was inflammatory and that is about as far as I can go I do not see how an area of constriction across this region such as Dr Wyman described can come from a vascular structure I had thought of aneurysm of the abdominal aorta, but that does not fit this, does it?

DR WYMAN No, but it fits with dilated common duct pressing on the duodenum

DR CHAPMAN I cannot do any better than this We might give someone else in the audience a chance

DR JACOB LERMAN What did the X-ray Department think it was?

DR BENJAMIN CASTLEMAN They thought it was inflammatory

DR CHAPMAN I did not mention retroperitoneal lymphoma I considered the possibility of a tumor of the lymphoma series involving the head of the pancreas and pressing on the duodenum

DR HOWARD B SPRAGUE Could it have started with pancreatitis?

*Davidson L S P and Smith, J Weil's disease in fishworkers clinical chemical and bacteriological study of 40 cases *Quart J Med* 5 263 286 1934

DR CHAPMAN An inflammatory mass subsequent to ordinary pancreatitis? Yes, that is perfectly possible. My first choice is an inflammatory mass, with pancreatic destruction. That fits the laboratory evidence best, and what lies behind that remains to be seen.

DR WYMAN There is a suggestion that this is well localized, so that I should place more emphasis on common-duct stone with secondary dilatation of the common duct or a tumor of the ampulla of Vater or the distal end of the common duct. However, a carcinoma of the pancreas or, I suppose, an inflammatory mass could look exactly the same.

DR CASTLEMAN Have you any comment, Dr Boyd?

DR WILLIAM BOYD (Toronto) I think pancreatitis of some type might be all right.

DR LYMAN DUFF (Montreal) The possibility of pancreatic cyst might be suggested, that is no more impossible than any of the other suggestions made.

DR KRANES I saw this patient on only one occasion about one month after he became ill in the other hospital. At that time he was on the mend, the jaundice diminishing, his appetite, which had previously been very poor, had increased enormously, and in general he was a great deal better. The history at the time—jaundice, nausea and fever, followed by the subsidence of the jaundice and the return of the appetite—was fairly characteristic of acute hepatitis. I might say in further support of that diagnosis that he was rather tender in the right upper quadrant. That is not brought out well in the history. The only thing that disturbed us was the fact that the fever occurred about two or three weeks after the onset of the jaundice rather than preceding the jaundice, and the laboratory tests were those of obstructive jaundice. Since he was improving it was decided to let him go home and see if he continued to improve. As the history brings out, although the appetite remained good he continued to lose weight, his jaundice grew more intense and repeated cephalin-flocculation tests done during this period were negative. So he was readmitted to the hospital with a diagnosis of obstructive jaundice. When he arrived on the ward everyone who saw him from students to house officers and visiting physicians all thought he had hepatitis until the results from the laboratory work were returned and the impressions were changed.

CLINICAL DIAGNOSIS

Infectious hepatitis?
Obstructive jaundice?

DR CHAPMAN'S DIAGNOSIS

Inflammatory mass in region of head of pancreas

ANATOMICAL DIAGNOSIS

Adenocarcinoma (low grade) of ampulla of Vater

PATHOLOGICAL DISCUSSION

DR CASTLEMAN The operation on the tenth day was an aspiration of the liver, which showed evidence of biliary obstruction. The bile ducts were all distended with bile. There was no doubt of an obstructive jaundice, and with that diagnosis Dr Linton operated. He found a large, distended gall bladder, the head of the pancreas felt pretty hard, but a rush frozen section on a biopsy showed normal pancreas. The common duct was markedly thickened and dilated, probably two or three times the normal size, this was strong evidence that there was an obstruction at the ampulla. The duodenum was therefore opened, disclosing a papillary lesion surrounding the papilla of Vater. A Whipple operation, which consisted in removing the head of the pancreas and duodenum and anastomosing the end of the common duct into the jejunum, was then performed.

The specimen we received showed a papillary tumor measuring $\frac{1}{2}$ cm in diameter probably arising in the duodenum, completely surrounding the ampulla and producing complete obstruction. The center of the tumor was at the ampulla. Histologically this was a slowly growing adenocarcinoma with very little invasion. We found one spot where it had gone beyond the muscularis mucosa, but there was no invasion of the pancreas at all.

Following operation the patient developed a localized abscess which was drained, and he is apparently doing well. A dozen regional lymph nodes were examined, and they were all normal. I am quite certain that there are no metastases.

CASE 35192

PRESENTATION OF CASE

First admission A seventy-five-year-old man was admitted to the hospital complaining of occasional abdominal pain and gaseous eructations.

Ten to twelve months previously he began having intermittent bouts of aching right-lower-quadrant pain, usually occurring at night. Six months before admission these pains became sharp and crampy and were severe enough to interfere with his sleep. They usually lasted two or three hours and were relieved somewhat by enemas. He had always been somewhat constipated, and he noted no change in the character of the stools. A system review was negative except for occasional slight ankle edema and some urinary frequency. Approximately one month before entry a complete checkup, including a gall-bladder and large-bowel x-ray series, was reported as negative in an outside hospital. A pulsating mass in the left upper

quadrant was found, and he was referred to this hospital

Physical examination was entirely negative except for a pulsating, 10-cm, rounded mass in the left upper quadrant, presenting just below the costal margin

The temperature was 98.6°F, the pulse 60, and the respirations 20. The blood pressure was 140 systolic, 80 diastolic

Laboratory studies showed a cloudy urine, with a specific gravity of 1.012, with 4 white blood cells per high-power field in the spun sediment. The hemoglobin was 11.8 gm

Chest x-ray films disclosed enlargement of the heart in the region of the left ventricle and a tortuous, elongated aorta. Plain films of the abdomen demonstrated a smooth mass, extending from the level of the twelfth thoracic vertebra about 9.5 cm to the left of the midline. There was some calcification about the periphery of the mass. The left kidney was possibly displaced slightly laterally. The right kidney was not remarkable. On the third hospital day wiring of the abdominal aneurysm was done by means of a trocar needle inserted through the back. He was discharged one week later.

Final admission (six months later) The patient continued to have daily attacks of severe abdominal pain, which was sometimes burning, sometimes sharp and crampy and sometimes aching. He gradually developed increasing constipation, progressing to almost complete obstipation, and had episodes of vomiting two or three times a week. His appetite gradually diminished, and he lost considerable weight.

Physical examination showed slight icterus, a hard, irregular liver edge, extending four finger-breadths below the costal margin, and an 8-cm mass in the right lower quadrant. There was, again, the 10-cm, pulsating mass in the left upper quadrant. The abdomen was distended and tympanitic, with high-pitched peristaltic gurgles. There was ++ edema of the ankles. The patient became increasingly jaundiced and more listless and died.

DIFFERENTIAL DIAGNOSIS

DR RICHARD J. CLARK We are given the history of a seventy-five-year-old man whose symptoms started out approximately eighteen months prior to his final admission to the hospital. He had crampy abdominal pains all through this period, which were apparently somewhat related to constipation—not too definitely at first, but quite definitely later on. Various studies were made, including gall-bladder x-ray films and a barium enema, which were said to have been negative at that time. A pulsating mass was found in the left upper quadrant. He came into the hospital, and the diagnosis of aneurysm was apparently made. We are told that this was wired. We have to be suspicious when given such a flat-footed diagnosis,

but there seems little reason to doubt that the patient had an abdominal aneurysm. In spite of the wiring of this aneurysm, he had no relief of pain, and he went on developing increasing constipation, weight loss, anorexia and finally vomiting. He returned to the hospital following a progressively downhill course and on the second entry presented a mass in the right lower quadrant and a liver that had become enlarged and nodular. He died without any sudden dramatic event.

The problems presented here are twofold: the nature of the pulsating mass in the left upper quadrant and its relation to symptoms, and the nature of the mass in the right lower quadrant and its association with the abnormal liver and the course of events. May we see the x-ray films?

DR STANLEY M. WYMAN The films of the chest are not remarkable except to demonstrate a heart that is prominent in the region of the left ventricle and a somewhat tortuous thoracic aorta. The films of the abdomen show the wired aneurysm, and the soft-tissue mass extending peripherally to the right is well seen. The lateral view discloses calcification in the walls of the aneurysm itself. The only other thing of particular note is the increase in the size of the liver from the first admission to the second, when it appears to be definitely larger.

DR CLARK Is there any appreciable change in the appearance of the lesion?

DR WYMAN Both these films are taken after the wiring, about six months apart, and there is no definite change that I can see.

DR CLARK Can you follow the course of the abdominal aorta at all?

DR WYMAN The calcification here lies in the aneurysm. It is impossible to follow it with accuracy, but it seems to extend in this fashion. Down below, it is readily seen where it comes out to more or less normal caliber at the level of the fourth lumbar interspace. The aneurysm itself lies apparently between the twelfth thoracic and the fourth lumbar vertebra.

DR CLARK Dr Wyman has been kind to us in granting that this is an aneurysm. He has left relatively little doubt about that particular point.

This man obviously had arteriosclerosis. We have no record over the course of time of his having had hypertension. Possibly he had it at some time in the past, but he was not in congestive failure. I see no definite indication for making a diagnosis of hypertensive heart disease. Lacking evidence for any other etiologic factor, we may reasonably assume that this patient had an arteriosclerotic form of heart disease, with arteriosclerosis of the aorta. Certainly from the descriptions given we may assume that he also had an abdominal aneurysm. The question arises just where the aneurysm was located. The three commonest locations are the abdominal aorta, the splenic artery and the hepatic artery. From the description we might have suspected origin

from the splenic artery, but it seems quite definite from the size of the aneurysm and the x-ray appearance in relation to the abdominal aorta that the aneurysm arose from the aorta. The next question is, What was the etiology of the aneurysm? While many aneurysms are syphilitic in origin, those of the thoracic aorta are more apt to be syphilitic, whereas I believe it has been shown in this laboratory that the majority of intra-abdominal aneurysms are arteriosclerotic. Was a serologic test done?

DR TRACY B MALLORY Yes, and it was negative.

DR CLARK That would be further evidence that this probably was an arteriosclerotic aneurysm of the abdominal aorta. What relation did this aneurysm have to the patient's presenting symptoms? Aneurysms by themselves do not ordinarily produce pain. Pain and other symptoms of aneurysm are almost entirely caused by their effect upon adjacent structures, from erosion, pressure and the like. Symptoms from aneurysm in the abdomen are apt to be notably absent because there is plenty of room for expansion, and pressure symptoms are less likely to occur. I toyed with the thought of involvement of the ostia of various branches of the aorta leading to the mesentery. Could this symptomatology have been related to what has been described as abdominal angina secondary to arteriosclerosis of abdominal vessels? It seems to me that in view of subsequent evidence there is no need to bring in any such supposition. I do not believe that the aneurysm had any important relation either to the patient's death or to the patient's symptoms, although symptoms of nausea, anorexia and so forth have been attributed to such lesions.

On the final entry we are given very few facts and almost no specific data on which to confirm or establish a diagnosis. Apparently no x-ray studies were done and no laboratory data are at hand. We do have the appearance of a tumor that had arisen in the right lower quadrant, and we have evidence of involvement of the liver. There are no data on which to substantiate a diagnosis of infection; nothing is said about tenderness in the mass or in the liver; there is no record of fever or leukocytosis. This leads us almost certainly to a neoplastic lesion. We might go through all the neoplasms in the lower abdomen that could metastasize to the liver, but in view of the rather definite symptoms of increasing constipation, weight loss

and so forth, without further ado we might just as well make the assumption that this patient had carcinoma of the colon, most likely in the region of the cecum, with metastases to the liver, and that he probably died as a result of this. The lesion was likely present but undiscovered at the time of the first x-ray examination. I cannot reasonably relate the aneurysm with the right-lower-quadrant mass or the liver. That leaves me with a diagnosis of arteriosclerotic heart disease, arteriosclerotic aorta, with an arteriosclerotic aneurysm of the abdominal aorta together with carcinoma of the colon and metastases to the liver.

CLINICAL DIAGNOSES

Carcinoma of colon, with metastases to liver
Abdominal aneurysm
Arteriosclerosis

DR CLARK'S DIAGNOSES

Carcinoma of colon, with metastases to liver
Arteriosclerotic aneurysm of abdominal aorta

ANATOMICAL DIAGNOSES

Carcinoma of ascending colon, with metastases to liver, regional lymph nodes, lungs and kidney
Arteriosclerotic aneurysm of abdominal aorta, wired
Arteriosclerosis, generalized, severe
Bronchopneumonia,
Pulmonary emboli, small
Thrombosis, periprostatic plexus of veins

PATHOLOGICAL DISCUSSION

DR ROBERT R LINTON I would like to compliment Dr Clark on his presentation of this case. He has described everything that I know about it. I will show some color slides, which will confirm his diagnosis. This first slide is a view of the abdomen when it was opened at autopsy. It shows a huge liver. Here is the left lobe with the metastatic nodules in the liver itself. There is nothing else of note in that view. This is the cut section of the liver. Much of the liver tissue was replaced or pushed aside by this tremendous infiltration of metastatic disease. The next slide shows the aorta and the aneurysm, the abdominal aneurysm, which has been wired. The next view shows the aorta when it has been opened. We have been unable to obtain many such specimens after wiring. There is a dark area that contains many of the loops of wire and

fresh blood clot, which is post-mortem clot. This portion out here is a gristle-like, partially organized thrombus. The wiring did what it was supposed to do—that is, it strengthened the wall of the aneurysmal sac so that it did not perforate and through it a channel led whereby blood could flow freely to the lower part of the body in spite of numerous coils of steel wire. The next is a closer view, showing the channel through which the blood flowed.

I became interested in the wiring of aneurysms because of the fact that we have a certain number of arteriosclerotic aneurysms that are the cause of a patient's death. Having watched a number of them perforate or rupture, and watched the patient suddenly expire, it seemed that one was justified to try almost anything to save their lives. Wiring of aneurysms dates back many years. I do not know who was the first courageous surgeon to attempt it, but it fell into disrepute chiefly because surgeons did not have the proper type of wire to use. The difficulty with the wire used formerly was that it was too stiff and rigid and followed the path of least resistance and ended up where one did not want it to go. The wire I have used is stainless steel, No 30 gauge, and very flexible so that it coils around without traveling up and down the aorta.

We must rely on preoperative x-ray studies to determine the cause of many patients' symptoms. If an abdominal arteriosclerotic aneurysm is found on examination I would like to warn that very often it is nothing but a red herring, and the cause of the symptoms is some other disease. In the case under discussion I unfortunately relied on a single x-ray examination taken at another hospital. The patient had had a barium enema and a gastrointestinal series, and the x-ray studies were reported as negative. I took that to be true and, as a result, decided to wire this aneurysm from a lumbar approach, which necessitates only a nick of the skin to insert the wiring trocar, and with this approach one can wire the abdominal aorta just as well from behind as in front. I did the wiring last June thinking that the aneurysm was the cause of the symptoms, as did his local physician. It was not until the patient developed a mass in the right lower quadrant that we decided to reinvestigate his gastrointestinal tract, and on a more careful search we found a lesion in the cecum, which Dr Wyman also demonstrated by roentgenologic examination a short time before the patient's death.

The lesson I learned from this case was not to rely on a single gastrointestinal series in a patient who has symptoms that do not seem typical of an abdominal aneurysm. I thought I was very smart a little while later because I had another patient come to me the latter part of last year. This patient was sixty-three years old, he was referred to me because of a mass in the abdomen, which obviously was the same kind of lesion, an arteriosclerotic abdominal aneurysm, which one can see in the x-ray films has been wired. His symptoms were those of obstruction—for six years he had had discomfort after eating heavy, fatty meals. The aneurysm was noted about one month before he came to me and during the last two weeks had increased in size. It seemed to me that his symptomatology suggested something wrong with his gastrointestinal tract, so I had a gastrointestinal series performed. The report came back that this mass was a prepyloric ulcer on the lesser curvature. Do you agree, Dr Wyman?

DR STANLEY M. WYMAN: It looks like it.

DR LINTON: I believe there was no question of correctness of this diagnosis since we all thought this man's symptoms were due to the prepyloric ulcer, so I transferred him to an internist for treatment of the prepyloric ulcer and determined to forget about the aneurysm for the present. A few days after the internist saw him the patient began to complain of terrific pain in the back, radiating to the groins. The aneurysm increased in size, and it was obvious that it was beginning to rupture and for that reason we did an emergency laparotomy and wired the aneurysm. Since then the pain in the groin and back disappeared. Here was a man with two lesions—the one that brought him to the hospital was the abdominal aneurysm, although the history was that of prepyloric ulcer. I have another that I would like to show. This is a sixty-five-year-old man who came to me in December. The chief complaint was indigestion. I took one look at him and said, "This man is not coming to me because of his aneurysm, he is coming to me because he has something else wrong with him." Examination revealed a large arteriosclerotic abdominal aneurysm. It was my opinion, however, that the man had a gastric lesion, and I thought that it probably was malignant. I referred him to the hospital, and the first thing done was a gastrointestinal series, which was reported negative. Because the pain was atypical for aneurysm, we thought of doing a Graham test, which showed a

number of calculi in the gall bladder. We finally decided to operate on him to take out the gall bladder and wire the aneurysm at the same time. To my consternation, when I opened his abdomen I found that he had a huge carcinoma of the stomach involving the fundus, which necessitated a total gastrectomy. So I ended up by doing that and let the aneurysm alone. I did not think it was justifiable to do both procedures at the same time. Another patient, referred to me by Dr. Arthur W. Allen, said that he was lying in bed one night, reading a book, and he noticed that it jumped up and down with every heart beat, and he became interested and found that he had an aneurysm. He had no symptoms whatever except the mass that kept bouncing up and down. In his case the aneurysm was successfully wired. Even after a most careful x-ray workup I still think that if one is going to wire an abdominal aneurysm (and I believe they should be wired because they probably will rupture sooner or later) it should be done through an abdominal exploratory incision rather than through the back with a small incision. In that way one can pick up a certain number of these patients who have other diseases and correct them and perhaps later on take care of the aneurysm.

DR. CLARK: Was the original lesion in the cecum?

DR. MALLORY: It was in the ascending colon, just above the cecum — there were extensive metastases to the liver and generalized, diffuse arteriosclerosis.

DR. CLARK: Did the heart show anything more?

DR. MALLORY: Nothing except diffuse coronary sclerosis without infarction.

DR. LINTON: In defense of the original barium-enema examination, I do not believe anyone would have found the tumor at the time it was done. Even before death the lesion was not too obvious or large at autopsy.

DR. WYMAN: In defense of the first examiner who saw the patient, the lesion must have been small because when I saw the films seven months later, before death, it was only 5 cm. in length.

DR. LINTON: I even shudder to think that I might have missed it had I done an exploratory laparotomy.

DR. CLARK: How much hazard is there involved in doing a wiring of this sort — do you have any way of knowing what the results are? Have you followed enough patients over a period to know how much good is accomplished?

DR. LINTON: I think that is hard to answer. I had a long letter from Dr. Cole, of England, who developed a wiring apparatus, and he said that he had spent his life trying to determine whether wiring of aneurysms prolonged life, and he was going to die without accomplishing it. It is difficult to say. There is a man from Atlanta, Georgia, in the hospital now with an abdominal aneurysm. The aneurysm began to leak while he was motoring through Connecticut. He was rushed to a hospital and referred here for treatment. I think, without question, that he would not have lived if the aneurysm had not been wired at that time. The thing that encourages me most to continue this treatment is that the autopsy in the case under discussion today showed that one can strengthen the wall and prevent it from perforating by this method.

DR. CLARK: What is the risk of the procedure?

DR. LINTON: The mortality is zero. I have done about 15 or 20 operations, which brings it down to a fairly reasonable risk. However, I am sure I will never do another through the back, no matter how sure we are by preoperative studies that that is the only trouble the patient has.

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ALL ROADS LEAD TO WORCESTER

THE one hundred and sixty-eighth annual meeting of the Massachusetts Medical Society will be held at the Worcester Memorial Auditorium on May 24, 25 and 26. This will be the first meeting away from Boston in a decade, the last out-of-town meeting having been held in Worcester in 1939.

The quality of the meetings of the Society has improved steadily since the war, and their popularity has increased out of all proportion to the increase in the Society's membership. In 1947, 1521 fellows and guests registered their attendance, and in 1948, 2436. While a meeting outside Boston does not ordinarily attract the numbers that a meeting in the more densely populated section

of the state can draw, every effort is being made to secure an especially large attendance this year.

As usual, the Council of the Society will meet on Monday evening, the day before the sessions begin, at the Hotel Sheraton. On the following morning, at 8:55, the first general session will convene in the Little Theater of the Memorial Auditorium. General sessions will continue to be held each morning and afternoon through Thursday, May 26.

The annual meeting of the Society will take place in the Memorial Auditorium at 11:00 on Tuesday morning, May 24. The annual oration, "Some Responsibilities of Medical Education," by Dr. C. Sidney Burwell, dean of the Harvard Medical School, will immediately follow. At the close of the oration the annual luncheon will be served. The Worcester District Medical Society has invited all members of the Massachusetts Medical Society to "Worcester Hofbrau Night" that evening, in the ballroom of the Sheraton. As if any inducements to attend were necessary, free entertainment will be furnished, and free beer will be served.

The Shattuck Lecture, always an event of great interest, will be delivered on Wednesday morning at 11:05 by Dr. Paul D. White, clinical professor of medicine at the Harvard Medical School, consultant in medicine at the Massachusetts General Hospital, and executive director of the National Advisory Heart Council. His subject is "La médecine du coeur."

The high point of the meeting will be the annual dinner on the evening of May 25, to which ladies may be invited. Tickets for the dinner, the fellows are warned, **MUST** be procured in advance. The speaker of the evening will be Roscoe Pound, LL.D., University Professor Emeritus, Harvard University, and former dean of the Harvard Law School, on the subject, "The Professions in the Society of Today."

The usual section meetings and luncheon will round out the program, and as usual the scientific and technical exhibits and the exhibition of works of art by members of the Massachusetts Physicians' Art Association will be well worth visiting.

This year, also, the Woman's Auxiliary will be on the scene as a full-fledged, functioning organ-

number of calculi in the gall bladder. We finally decided to operate on him to take out the gall bladder and wire the aneurysm at the same time. To my consternation, when I opened his abdomen I found that he had a huge carcinoma of the stomach involving the fundus, which necessitated a total gastrectomy. So I ended up by doing that and let the aneurysm alone. I did not think it was justifiable to do both procedures at the same time. Another patient, referred to me by Dr. Arthur W. Allen, said that he was lying in bed one night, reading a book, and he noticed that it jumped up and down with every heart beat, and he became interested and found that he had an aneurysm. He had no symptoms whatever except the mass that kept bouncing up and down. In his case the aneurysm was successfully wired. Even after a most careful x-ray workup I still think that if one is going to wire an abdominal aneurysm (and I believe they should be wired because they probably will rupture sooner or later) it should be done through an abdominal exploratory incision rather than through the back with a small incision. In that way one can pick up a certain number of these patients who have other diseases and correct them and perhaps later on take care of the aneurysm.

DR. CLARK: Was the original lesion in the cecum?

DR. MALLORY: It was in the ascending colon, just above the cecum — there were extensive metastases to the liver and generalized, diffuse arteriosclerosis.

DR. CLARK: Did the heart show anything more?

DR. MALLORY: Nothing except diffuse coronary sclerosis without infarction.

DR. LINTON: In defense of the original barium-enema examination, I do not believe anyone would have found the tumor at the time it was done. Even before death the lesion was not too obvious or large at autopsy.

DR. WYMAN: In defense of the first examiner who saw the patient, the lesion must have been small because when I saw the films seven months later, before death, it was only 5 cm. in length.

DR. LINTON: I even shudder to think that I might have missed it had I done an exploratory laparotomy.

DR. CLARK: How much hazard is there involved in doing a wiring of this sort — do you have any way of knowing what the results are? Have you followed enough patients over a period to know how much good is accomplished?

DR. LINTON: I think that is hard to answer. I had a long letter from Dr. Cole, of England, who developed a wiring apparatus, and he said that he had spent his life trying to determine whether wiring of aneurysms prolonged life, and he was going to die without accomplishing it. It is difficult to say. There is a man from Atlanta, Georgia, in the hospital now with an abdominal aneurysm. The aneurysm began to leak while he was motoring through Connecticut. He was rushed to a hospital and referred here for treatment. I think, without question, that he would not have lived if the aneurysm had not been wired at that time. The thing that encourages me most to continue this treatment is that the autopsy in the case under discussion today showed that one can strengthen the wall and prevent it from perforating by this method.

DR. CLARK: What is the risk of the procedure?

DR. LINTON: The mortality is zero. I have done about 15 or 20 operations, which brings it down to a fairly reasonable risk. However, I am sure I will never do another through the back, no matter how sure we are by preoperative studies that that is the only trouble the patient has.

group than in the controls. The typhoid strain responsible for the outbreak was no more resistant to the action of penicillin and sulfathiazole than other strains with which it was compared *in vitro*. Bevan and his co-workers therefore considered it necessary to warn against the indiscriminate use of penicillin and sulfathiazole in the treatment of typhoid fever.

McSweeney was sufficiently impressed with the bacteriologic effects of the penicillin and sulfathiazole therapy in his cases to suggest that the same regime be tried in attempts to clear up typhoid carriers. Comerford,⁶ following this lead, used both sulfathiazole and penicillin on 2 known carriers who regularly excreted typhoid bacilli even after cholecystectomy. He used 2 gm of sulfathiazole followed by 1 gm every 4 hours by mouth, and 500,000 units of penicillin intramuscularly at the same interval. This was continued for seven or eight days, and in both patients the stool cultures remained free of typhoid bacilli for a follow-up period of about four months. In another study, however, Fry and his associates⁷ used the same regime in 17 chronic fecal carriers. There were only 3 apparent successes. In 2 of the cases in which the usual doses had failed, doses of 40,000,000 units and 12 gm of sulfathiazole per day were given on three occasions and proved unsuccessful. These workers concluded that the therapeutic results of the penicillin and sulfathiazole treatment in typhoid carriers were not encouraging.

The introduction of streptomycin raised new hopes for effective therapy in typhoid fever because of the susceptibility of the organisms to this antibiotic *in vitro*. Reimann, Elias and Price⁸ treated 5 patients with severe typhoid fever, and on doses of 1 to 4 gm per day intravenously or intramuscularly obtained levels of streptomycin in the blood and urine that were more than sufficient to kill the organisms *in vitro*. Small quantities of the antibiotic were also excreted in the feces. Both parenteral and oral administration of streptomycin was considered desirable, the former to control the bacteremia and bacilluria and the latter to sterilize the feces and prevent reinfection and the carrier state. There was no evidence of the development of increased resistance during exposure of the or-

ganisms to streptomycin in the body. However, only 3 of the 5 patients recovered, and, in addition, bacilemia and positive stool cultures persisted in some cases in spite of the exposure of the organisms to concentrations of streptomycin greater than that required to kill the organisms *in vitro*.

Since this study of Reimann and his associates, it has been amply demonstrated that streptomycin has little if any favorable effect on the clinical and bacteriologic course of typhoid fever. The 169 cases collected by Keefer and Hewitt⁹ seemed to bear this out.

Of interest is the failure in most cases of typhoid fever to demonstrate the development of resistance in organisms that persist in the blood and stools during treatment with streptomycin. Comparable observations have been made by Hall and Spink¹⁰ in cases of brucellosis. Such findings suggest either the failure of the antibiotic to obtain access to the bacteria or possibly a difference in the genetic constitution of these organisms that affects the mutations concerned in the development of streptomycin-resistant flora. Of additional interest is the demonstration of "hormesis" (an increase in the mortality rate) among mice infected with typhoid bacilli and treated with subeffective concentrations of either penicillin¹¹ or streptomycin.¹² The immunity that followed the typhoid infection in the streptomycin-treated mice that recovered suggested that when the small doses of drug were used, there was actually multiplication of the organisms *in vivo*.

It is natural that new antibiotics that are relatively nontoxic and have a definite effect on gram-negative bacilli *in vitro* and in experimental infections should receive a clinical trial in the treatment of typhoid fever. Preliminary trials of two such antibiotics have appeared recently. Ten cases of typhoid fever were treated with chloromycetin¹³ in Kuala Lumpur during the course of clinical trials with this agent in scrub typhus. The course of the typhoid fever was markedly shortened in comparison with that in untreated cases, and the febrile stage of the illness was terminated in an average of three and a half days after treatment was begun. These patients were treated orally with an initial dose of 50 mg per kilogram of body weight,

ization, with all but one or two districts participating. With a year's experience since its organizational meeting, it will hold its first annual meeting on May 24 at the Worcester Woman's Club.

All roads lead to Worcester, come one, come all!

ANTIBIOTIC THERAPY OF TYPHOID FEVER

TYPHOID fever is one of the few acute bacterial infections in which modern chemotherapy has not yielded very brilliant results. It is generally agreed that the sulfonamide drugs have no effect whatever on the course of this disease, although they exert a definite bacteriostatic effect on the causative organisms *in vitro*. There have, however, been some conflicting claims concerning the effects of the combined use of penicillin and sulfonamides, and there are indications that some of the newer antibiotics may be beneficial. Since this disease, because of its possible severity in the individual patient and because of its public-health aspects, may assume importance out of proportion to its frequency, it may be of interest to review some of the recent reports on the effects of chemotherapy.

It is now generally appreciated that many gram-negative bacilli and particularly the typhoid bacilli are not totally resistant to the action of penicillin. They are essentially like the less sensitive strains of staphylococci in that they require relatively high concentrations to inhibit their growth. Evans¹ found that most strains of this organism were inhibited by 5 to 10 units of penicillin per cubic centimeter, and Welch and Randall² reported that all but 1 of 29 strains of typhoid bacilli tested were inhibited by 12 units or less of penicillin G, and all 29 were inhibited by 6 units of penicillin X.

In vitro studies carried out by Bigger³ showed that penicillin in concentrations up to 8 units per cubic centimeter reduced but did not prevent the growth of *Escherichia typhosa* in broth. Sulfathiazole in concentrations up to 10 mg per 100 cc inhibited the multiplication of these organisms, but a bactericidal effect was obtained only when small numbers of bacteria were exposed. The combination of penicillin and sulfathiazole, however, had a pronounced bactericidal effect. Thus, a concentration of 4 units of penicillin per cubic centimeter

and 10 mg of sulfathiazole per 100 cc sterilized a culture inoculated with 70,000 typhoid bacilli per cubic centimeter, and 1 unit of penicillin with the same amount of sulfathiazole sterilized a culture inoculated with 7000 organisms per cubic centimeter. On the basis of his findings, Bigger suggested a tentative therapeutic regime for the treatment of typhoid fever. This consisted of full doses of sulfathiazole in addition to penicillin in doses of 2,500,000 to 3,000,000 units per day by continuous drip for five to seven days. This dosage would be expected to maintain a concentration of 2 units of penicillin per cubic centimeter of blood. Both these agents would be given again if typhoid organisms reappeared in blood or stools.

Following this suggestion McSweeney⁴ treated a series of 6 severe cases. One of his patients who received doses of penicillin appropriate for ordinary staphylococcal infections showed no appreciable effect on the pyrexia or blood cultures, although the toxemia was much lessened. The other 5 patients were treated intensively with penicillin and sulfathiazole and received two courses, each comprising 10,000,000 units of penicillin and 34 gm of sulfathiazole in four days. Speedy disappearance of toxemia, subsidence of pyrexia and disappearance of organisms from the blood, feces and urine followed the end of the second course in 4 of these 5 patients. McSweeney regarded the clinical effects observed as confirming the laboratory findings of Bigger.

In a later and somewhat more extensive study, Bevan and his co-workers⁵ treated 39 patients with penicillin and sulfathiazole in doses comparable to those used by McSweeney. The cases all occurred in a single outbreak. These workers did not observe the speedy disappearance of toxemia and subsidence of fever described by McSweeney. In the cases treated by this method, there was no evidence of any appreciable clinical effect of the drug treatment when compared with comparable cases in which the patients did not receive this therapy. Furthermore, a considerable proportion of the patients yielded positive blood cultures shortly after completion of the course of penicillin and sulfathiazole, and fecal excretion of typhoid bacilli during convalescence was not shorter in the treated

MASSACHUSETTS MEDICAL SOCIETY ANNUAL MEETING OF THE COUNCIL

The annual meeting of the Council of the Massachusetts Medical Society will be held at the Sheraton Hotel, Worcester, on Monday, May 23, 1949, at 7:00 p m

Business

- 1 Call to order at 7 00 p m
- 2 Presentation of record of meeting held February 2, 1949, as published in *The New England Journal of Medicine*, issue of April 2, 1949
- 3 Reports of standing and special committees
- 4 Report of Committee on Nominations

President DR ARTHUR W ALLEN

President-Elect DR LELAND S MCKITTRICK

Vice-President DR ALBERT A HORNER

Secretary DR H QUIMBY GALLUPE

Treasurer DR ELIOT HUBBARD, JR

Assistant Treasurer DR NORMAN A WELCH

Orator DR JOHN W O'MEARA

- 5 Such other business as may legally come before this meeting

Councilors are asked to sign one of the two attendance books before the meeting. The Cotting Supper will be served immediately before the meeting.

H QUIMBY GALLUPE, M D
Secretary

DEATH

CUMMINGS — Morton E Cummings, M D, of Malden died on April 20. He was in his seventy-fourth year. Dr Cummings received his degree from Harvard Medical School in 1901.

His widow and a daughter survive.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Abdominal Operations. By Rodney Maingot, F R C S, surgeon to the Royal Free Hospital, London, and to the Southend General Hospital. Second edition, 8° cloth, 1274 pp, with illustrations. New York: Appleton-Century-Crofts, Incorporated, 1948. \$16 00.

This treatise on surgery of the abdomen and its organs is the joint work of Dr Maingot and eight collaborators. Although the treatise is written by English surgeons with the exception of Dr Dragstedt, of the University of Chicago, and Dr Harrington, of the Mayo Foundation, the book was printed in the United States. The whole text has been thoroughly revised and brought up to date since the publication of the last edition. Many illustrations for new and revised operations have been added. Pertinent references have been interpolated throughout the text. The material is well arranged. A very good large type has been used, and the illustrations are excellent. The book is recommended for medical libraries and should be available to all persons interested in surgery of the abdomen. It should be recognized as a standard treatise in its field.

Diseases of the Ear, Nose and Throat. By William W Morrison, M D, professor of otolaryngology and attending otolaryngologist, New York Polyclinic Medical School and

Hospital senior assistant surgeon in otolaryngology, New York Eye and Ear Infirmary, and associate clinical professor of otolaryngology, New York University College of Medicine. 8°, cloth, 772 pp, with 359 illustrations. New York: Appleton-Century-Crofts, Incorporated, 1948. \$8 50.

This new textbook, written for the undergraduate medical student and the general practitioner, is based on a long period of teaching. The text is divided into eight parts. The first is devoted to general considerations, including history taking, equipment for examination and chemotherapy in otolaryngology. The other parts, in order, deal with diseases of the ear, diseases of the external nose and the nasal cavities, allergic diseases of the respiratory tract, and diseases of the paranasal sinuses, of the throat, of the larynx, and of the trachea, bronchi, esophagus and mediastinum. An appendix comprises a formulary of prescriptions for medications to be used by patients. The volume concludes with two indexes of subjects and symptoms. The material is well organized, and the text well written. Lists of selected references are appended to the chapters. The illustrations are original with the author. The book is well published and should prove useful as a reference source.

Streptomycin and Tuberkulose. Herausgegeben von G Fancioni und W Löffler unter Mitwirkung von J Barth et al. 8°, paper, 357 pp, with 233 illustrations. Basel, Switzerland: Benno Schwabe and Company, 1948. 30 Swiss francs.

This monograph is comprehensive and well written. The text is well arranged and consists of introduction and four major sections. The first discusses general problems influencing cellular respiration, the experimental groundwork, cytotoxic action, and the use of streptomycin, para-aminosalicylic acid and sulfone in experimental tuberculosis. The second deals with hematogenous spreading in tuberculous meningitis, miliary tuberculosis in the aged and in children and tuberculosis in infants and children. The third, comprising about half the text, considers tuberculosis of the various organs and of the lymph nodes, as well as fistulas. The fourth is devoted to the pathological anatomy of tuberculous meningitis and miliary tuberculosis after streptomycin treatment, and a description of 3 cases of osteomalacia occurring in tuberculous meningitis treated with streptomycin. The text is concluded with a large bibliography. The publishing is excellent in every way. There is an adequate table of contents, but the lack of an index detracts from the reference value of the book. The monograph is recommended for all medical libraries and to all persons interested in the subject.

Zinsser's Textbook of Bacteriology, The application of bacteriology and immunology to the diagnosis, specific therapy and prevention of infectious diseases for students and practitioners of medicine and public health. 8°, cloth, 992 pp, with 250 illustrations. Revised by David T Smith, M D, professor of bacteriology and associate professor of medicine, Duke University School of Medicine, Donald S Martin, M D, M P H, professor of preventive medicine and public health and associate professor of bacteriology, Duke University School of Medicine, Norman F Conant, Ph D, professor of mycology and associate professor of bacteriology, Duke University School of Medicine, Joseph W Beard, M D, professor of surgery in charge of experimental surgery, Duke University School of Medicine, Grant Taylor, M D, associate professor of bacteriology and associate professor of pediatrics, Duke University School of Medicine, Henry I Kohn, Ph D, M D, surgeon, United States Public Health Service, and assistant professor of physiology and pharmacology (on leave), Duke University School of Medicine, and Mary A Poston, M A, instructor in bacteriology, Duke University School of Medicine. Ninth edition. 8°, cloth, 992 pp, with 251 illustrations. New York: Appleton-Century-Crofts, Incorporated, 1948. \$10 00.

This standard textbook was first published in 1910. Through eight editions Drs Hiss, Zinsser and Bayne-Jones were responsible for the text. This edition has been thoroughly revised and brought up to date. The sections on bacterial metabolism, immunology and fungous and viral diseases have been rewritten entirely. A chapter on pleuropneumonia-like organisms and a section on the antibiotics have been added, and the material on the sulfonamides has been expanded.

followed by 0.25 gm every three or four hours and smaller doses after the temperature had been reduced. Concentrations of chloromycetin that were many times the bacteriostatic levels for the organisms were obtained in the serum.

Even in this small group of chloromycetin-treated cases, however, some of the reported observations indicate that the beneficial results were far from optimal. Positive stools were obtained in 2 patients during convalescence, 2 other patients had relapses of fever with positive blood cultures after being afebrile for ten to sixteen days, 1 patient had an intestinal perforation two days after the temperature had returned to normal, and another had a large hemorrhage from the bowel after being afebrile for four days.

Aureomycin is the most recent antibiotic to receive a trial in typhoid fever. This agent is effective against typhoid bacillus *in vitro*¹⁴ and in experimental infections.¹⁵ With this agent, although the results of treatment in some patients with typhoid fever seemed encouraging, the results in other patients were quite equivocal.¹⁴

Of these new agents chloromycetin appears to be more beneficial during the acute illness, but neither of these antibiotics, according to a number of unpublished reports, has any influence on the carrier state.

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STILL THE AMERICAN WAY

VOLUNTARY health insurance needs only time in which to earn the nation's full confidence. By the end of 1948, according to Blue Shield national headquarters, the enrollment in Associated Medical Care Plans had reached 10,370,819, having experienced its greatest quarterly gain, of 1,057,274 members, in the last quarter of the year. This increment represents a growth of 11.35 per cent for the short period mentioned.

Enrolled in this same period were approximately a quarter million Ford Motor Company employees. The majority of these joined Michigan Medical Service, which continues to be the largest plan in the country, with a peak 1948 enrollment of 1,311,811. The New York City Plan ranks second with 1,128,967 members listed.

Varying as Blue Shield plans must in different localities and under a variety of background conditions, there is nevertheless an average or "typical" plan. The average plan is described as providing "complete surgical and obstetrical care including delivery, fractures and dislocations, medical care for hospitalized cases, limited diagnostic x-ray, and anesthesia."

Average subscription costs are \$1.17 per month for a single subscriber, who is provided with the above mentioned benefits on a service basis if his annual income is less than \$2050, \$2.26 for a man and wife and \$2.75 for a family. The benefits are provided on a service basis for families with incomes less than \$3100.

A criticism directed against voluntary prepayment plans for medical care is that they do not provide complete coverage. This, in fact, should be considered as one of the chief points in their favor. Calculated on an actuarial basis they balance the benefits against the cost, operating on as economical a basis as possible. Like Blue Cross they do not absorb all the costs of illness but cushion the shock, making it possible for the average earner to meet the obligations that have been tempered by his insurance.

Until a real majority of the American people may decide otherwise this form of independence and self-reliance must still be considered as a vital part of the American heritage.

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HYPERCALCEMIA WITHOUT HYPERCALCURIA OR HYPOPHOSPHATEMIA, CALCINOSIS AND RENAL INSUFFICIENCY*

A Syndrome Following Prolonged Intake of Milk and Alkali

CHARLES H. BURNETT, M.D.,† ROBERT R. COMMONS, M.D.,‡ FULLER ALBRIGHT, M.D.,§
AND JOHN E. HOWARD, M.D.¶

BOSTON AND BALTIMORE

BECAUSE of our interest in the parathyroid glands our attention has been directed to a number of diseases with which primary hyperparathyroidism may be confused. These include acute osteoporosis,¹ hypervitaminosis D,^{2,4} sarcoidosis⁵ and myelomatosis,⁶⁻⁸ carcinomatosis with extensive bone involvement,⁶ polyostotic fibrous dysplasia,⁹ renal osteitis fibrosa generalisata¹⁰ and osteomalacia.¹⁰ By clinical and laboratory observations it is usually possible to differentiate these conditions from primary hyperparathyroidism. However, when the latter condition is complicated by secondary renal damage the diagnosis, in our experience, may be very difficult.^{6, 11} This report describes a syndrome observed in 6 patients that has many features in common with primary hyperparathyroidism and secondary kidney damage but that we now believe has an entirely different etiology.

The characteristic features in these patients are a history of prolonged and excessive intake of milk and absorbable alkali, hypercalcemia without hypercalcuria or hypophosphatemia, normal serum alkaline phosphatase level, marked renal insufficiency with azotemia, mild alkalosis, calcinosis manifested especially by an ocular lesion resembling band keratitis, and an improvement in the clinical state on an intake low in milk and absorbable alkali.

CASE REPORTS

CASE 1. A. McA. (M. G. H. 235557) a 44-year-old caretaker was first admitted to the hospital in February 1940, complaining of pruritus of 3 years' duration. Since the age

of 11 he had suffered from epigastric pain relieved by food and sodium bicarbonate. Three years before admission, a peptic ulcer had been found on x-ray examination; subsequently he had been almost constantly on a regimen of several quarts of milk daily and large quantities of absorbable alkalis. Five years before admission, during a period of 3 months, he had had three attacks of renal colic with passage of gravel and stones. On a high fluid intake there had been no recurrence of these symptoms. Other significant points in the past history were spinal meningitis at the age of 21, and a heavy alcoholic intake for 30 years.

Physical examination disclosed a well developed and well nourished man. The corneas showed band keratopathy, the fundi were normal. The liver edge was just felt at the costal margin. The blood pressure was 140/80.

Routine urinalyses revealed a maximal specific gravity of 1.012, acid reactions and a ++ test for albumin. The sediment contained 10 to 15 white cells per high-power field, an occasional red cell and rare granular casts. Urine culture was negative. The phenolsulfonephthalein test demonstrated 15 per cent excretion of the dye 1 hour after intravenous injection. The Sulkowitch test showed no increase in calcium. A test for urinary Bence-Jones protein was negative. Examination of the blood disclosed a red-cell count of 4,350,000 with a hemoglobin of 85 per cent and a white-cell count of 9700 with a normal differential. There were no abnormal cells in the sternal bone marrow. The serum calcium was 12.4 mg, inorganic phosphorus 4.0 mg, alkaline phosphatase 5.3 Bodansky units, and nonprotein nitrogen 58 mg per 100 cc. The carbon dioxide combining power was 27.4 milliequiv per liter and the protein 9.8 gm per 100 cc.

A gastrointestinal series revealed a nonobstructing duodenal ulcer. Films of the skull showed normal bones.

A definite diagnosis was not made, but the patient was discharged on a reduced milk intake and advised to take no alkalis.

On his second and third admissions, both in October 1941, he complained of great weakness, continuing pruritus, polydipsia and polyuria. The ulcer had been asymptomatic, milk intake had averaged 2 or 3 glasses daily, and he had taken no alkalis. The physical examination revealed no changes from the previous admission. Examination of the urine was unchanged. The serum calcium was 12.0 to 14.6 mg and the phosphorus 4.0 to 4.7 mg per 100 cc. The alkaline phosphatase was 1.7 Bodansky units, the carbon dioxide content 31 milliequiv and the chloride 84.5 milliequiv per liter. The nonprotein nitrogen was 80 mg and the total protein 9.2 mg per 100 cc with an albumin of 5.6 gm and a globulin of 3.6 gm. Calcium and phosphorus balance was negative. The average urinary excretion of calcium was 87 mg per 24 hours.

Further x-ray studies demonstrated no evidence of decalcification in the skeleton. The lamina dura about the teeth was preserved.

*From the Evans Memorial Hospital, the Department of Medicine, Boston University School of Medicine, the Massachusetts General Hospital, the Department of Medicine, Harvard Medical School, and the Johns Hopkins University School of Medicine and Hospital.

†Assistant professor of medicine, Boston University School of Medicine.
‡Senior fellow, National Institute of Health, assistant in medicine, Eastern University School of Medicine.

§Associate professor of medicine, Harvard Medical School.

¶Associate professor of medicine, Johns Hopkins School of Medicine.

Likewise, 182 new illustrations, including many electron micrographs, have been included. Lists of pertinent references have been added to the various chapters. A good index concludes the volume. The book is recommended for all medical and public-health libraries and to all persons interested in bacteriology.

NOTICES

SOUTH END MEDICAL CLUB

A luncheon meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, May 17, at 12 noon. Dr. Francis J. Wenzler will speak on the subject "Pediatric Aspects of Erythroblastosis and Its Treatment."

Physicians are cordially invited to attend.

VERMONT STATE MEDICAL SOCIETY

The University of Vermont College of Medicine will be host to the Vermont State Medical Society for its annual meeting to be held in Burlington on May 19. The morning session will be held at the Bishop DeGoesbriand Hospital, and lunch and the afternoon sessions will be at the Mary Fletcher Hospital. Papers will be presented by various members of the university faculty.

MASSACHUSETTS GENERAL HOSPITAL

A special research meeting will be held in the Bigelow Amphitheater of the Massachusetts General Hospital on Monday, May 23, at 4:30 p.m. Dr. W. F. H. M. Mommaerts, of the Department of Biochemistry, Duke University School of Medicine, will speak on the subject "Fundamental Problems in Muscular and Cardiac Biochemistry."

NEW ENGLAND DIABETES ASSOCIATION

The annual meeting of the New England Diabetes Association will be held in Thayer Hall, City Hospital, Worcester, Massachusetts, on Monday, May 23, at 4 p.m.

CLINICAL PROGRAM

Neuropsychiatric Aspects of Diabetes Dr. Foster L. Vibber
Potential Diabetes Dr. Joseph A. Lundy
Necrotizing Papillitis in Diabetes Dr. Edward F. Ramsdell
Pathology of Necrotizing Papillitis Dr. Raymond H. Goodale
Experience with Diabetic Coma at Worcester City Hospital Dr. Albert E. Hall
Optimism and Diabetes Dr. George Ballantyne

The clinical program will be preceded by the annual business meeting including the election of officers and four directors. This meeting is planned in conjunction with the annual meeting of the Massachusetts Medical Society, May 23 to 26. The meeting will be completed in time so that councilors of the Massachusetts Medical Society can attend the Cotting supper at 6:00 p.m.

CONFERENCE OF PRESIDENTS AND OTHER OFFICERS OF STATE MEDICAL ASSOCIATIONS

The fifth annual Conference of Presidents and Other Officers of State Medical Associations will be held at Atlantic City on Sunday afternoon, June 5. The meeting, which will be held in the Rose Room of the Traymore Hotel on the day preceding the opening of the American Medical Association general sessions, will be open to all physicians. The meeting will be devoted to a discussion of compulsory health insurance plans for medical care and disability compensation.

CONFERENCE OF COUNTY MEDICAL SOCIETY OFFICERS

The fifth national Conference of County Medical Society Officers will be held in the Rose Room of the Hotel Tray-

more, Atlantic City, on Sunday, June 5. The conference will consist of three panel discussions on emergency calls, local places for medical care of the indigent and the national health campaign. At a session in the Trimble Room of the Claridge Hotel, Atlantic City, at 8 p.m., Mr. Clem Whitaker, director of the National Education Campaign of the American Medical Association, and the Honorable John L. McClellan, United States Senator from Arkansas, will be the speakers.

AMERICAN SOCIETY FOR THE STUDY OF STERILITY

The fifth annual conference of the American Society for the Study of Sterility will be held at the Hotel Strand, Atlantic City, on June 6 and 7. The two-day program will be divided into general discussions on the physiology of the uterus, new and known facts concerning reproduction and recent advances in reproduction and a round-table discussion on male sterility.

Additional information may be obtained from the program chairman (Dr. Fred A. Simmons, 330 Dartmouth Street, Boston 16, Massachusetts), the local arrangements chairman (Dr. Abner I. Weisman, 1160 Fifth Avenue, New York City) or the registration secretary (Dr. Walter W. Williams, 20 Magnolia Terrace, Springfield, Massachusetts).

INTERNATIONAL ACADEMY OF PROCTOLOGY

The first meeting of the International Academy of Proctology will be held at the Marlborough-Blenheim in Atlantic City, New Jersey, on Friday, June 10.

The scientific portion of the program will consist of the presentation of papers and motion-picture films of interest to all physicians as well as to those specializing in proctology.

Further information and a copy of the program may be obtained by application to Dr. Alfred J. Cantor, International Academy of Proctology, 43-55 Kissena Boulevard, Flushing, New York.

SOCIETY MEETINGS AND CONFERENCES

- MAY 16-19 American Urological Association Biltmore Hotel Los Angeles California
- MAY 17 South End Medical Club Notice above
- MAY 18-21 Association for Physical and Mental Rehabilitation Page 401 issue of March 10
- MAY 18-21 American Orthopaedic Association Page 702 issue of April 28
- MAY 19 Vermont State Medical Society Notice above
- MAY 23 Massachusetts General Hospital Notice above
- MAY 23 New England Diabetes Association. Notice above.
- MAY 23-27 American Psychiatric Association Page 668 issue of April 21
- MAY 24-26 Massachusetts Medical Society Annual Meeting Worcester Memorial Auditorium Worcester
- MAY 24-26 Massachusetts Physicians Art Association. Page 588 issue of April 7
- MAY 26-28 American Goutier Association Hotel Loraine Madison Wisconsin
- MAY 30-JUNE 3 International Congress on Rheumatic Diseases Page 800 issue of November 18
- JUNE 1-3 Academy of Neurology Page 588 issue of April 7
- JUNE 2-5 American College of Chest Physicians. Page 490 issue of March 24
- JUNE 3-5 Christian Medical Society Page xv issue of April 14
- JUNE 5 Conference of Presidents and Other Officers of State Medical Associations. Notice above
- JUNE 5 Conference of County Medical Society Officers. Notice above
- JUNE 6 and 7 American Society for the Study of Sterility Notice above
- JUNE 10 International Academy of Proctology Notice above
- JUNE 20-23 Annual Conference of Health Officers and Public Health Nurses Page xvii issue of February 3
- JUNE 20-23 American Society of Medical Technologists. Page 528 issue of March 31
- JUNE 30-JULY 2 American Association of Railway Surgeons. Page 490 issue of March 24
- SEPTEMBER 6-10 American Congress of Physical Medicine Page xiii issue of March 24
- SEPTEMBER 28-30 Mississippi Valley Medical Society Page 1060 issue of December 30

(Notices concluded on page xv)

not change. Symptomatically he was slightly improved on discharge.

He was not seen again at the Massachusetts General Hospital, failed progressively after discharge and died in July, 1943. No autopsy was performed, and the nature of the terminal illness is unknown.

CASE 3 C McC (M G H 324826), a 44-year-old married man, was first seen in October, 1941, complaining of intermittent claudication. A diagnosis of thromboangitis obliterans was made, and a left lumbar sympathectomy performed. Three routine urine specimens were entirely normal, the specific gravities varied between 1.002 and 1.014. A bi-

and duodenum. The bones of the hands and skull were normal. In the abdomen there was extensive calcification of both iliac arteries and calcification in the region of both kidneys, probably in the renal arteries, and in the aorta.

On a low calcium diet and high fluid intake the patient was much better subjectively, and the pruritus diminished remarkably. Coincident with the clinical improvement the serum calcium fell to 11.4 mg and the nonprotein nitrogen to 52 mg per 100 cc.

In May, 1947, on a follow-up visit, the serum calcium was 10.6 mg, the phosphorus 2.3 mg, and the nonprotein nitrogen 64 mg per 100 cc. During several visits between December, 1947, and February, 1948, the serum nonprotein ni-

TABLE 1 Summary of Renal-Function Tests

CASE No	DATE	GLOMERULAR FILTRATION*	EFFECTIVE PLASMA FLOW	MAXIMAL TUBULAR EXCRETORY CAPACITY	FILTRATION FRACTION	RATIO OF GLOMERULAR FILTRATION TO MAXIMAL TUBULAR EXCRETORY CAPACITY	PHENOLSULFONE-PHTHALEIN EXCRETION	STANDARD UREA CLEARANCE
		cc / 1.7 sq m / min	cc / 1.73 sq m / min	mg / 1.73 sq m / min			cc	%
1	—	—	—	—	—	—	5 (in 15 min)	—
2	—	—	—	—	—	—	20 (in 2 hr)	—
3	—	41	141	6	0.29	6.5	3 (in 1 hr)	—
4	—	—	—	—	—	—	8 (in 30 min)	25
5	9/10/47	—	—	—	—	—	5 (in 1 hr)	—
	8/19/47	20	48	2.5	0.42	8.0	—	—
	5/27/48	21	60	4.0	0.35	5.2	—	—
6	1/19/48	34	136	17.1	0.25	2.0	10 (in 2 hr)	—
	3/29/48	40	172	—	0.22	—	—	—
Normal values		130	700	75.0	0.19	1.7	—	—

*Glomerular filtration rates were measured with mannitol in Cases 4 and 5 and with inulin in Case 6. Effective plasma flow and maximal tubular excretory capacity were determined with sodium para amino hippurate. (We are indebted to Dr W P Boger of Sharp and Dohme Inc. for generous supplies of mannitol and sodium para amino hippurate.)

opsy taken from the left kidney at the time of operation revealed normal renal tissue.

The patient had been told 25 years previously that he had a peptic ulcer. Since then milk and antacids had been frequently employed to control symptoms.

In May, 1943, he entered another hospital in uremia. A serum nonprotein nitrogen of 198 mg per 100 cc, a low urine specific gravity and a + test for albumin were reported at this time. With parenteral administration of fluids he improved and was discharged.

In November, 1946, the patient again entered the Massachusetts General Hospital because of exacerbation of ulcer symptoms, nervousness, fatigue, nausea and intractable pruritus. He had continued to take large quantities of milk and variable amounts of alkali.

Physical examination showed a thin haggard man with a sallow complexion. The eyes disclosed band keratopathy and normal fundi. The only arterial pulsation palpable in either leg was that of the right femoral artery. The left arm and leg were warmer than the right. The blood pressure was 170/105.

Routine urinalysis demonstrated a maximal specific gravity of 1.011, a ++ test for albumin and a pH of 6.0 to 7.5. The sediment contained rare hyaline and granular casts and occasional red cells and white cells. Urine cultures revealed a moderate growth of *Staphylococcus albus* and *aureus*, but were negative for pleuropneumonia-like organisms. The urine calcium excretion was 109 mg per 24 hours. The results of renal-function studies are presented in Table 1.

Examination of the blood showed a red-cell count of 4,050,000 with a hemoglobin of 10 gm and a white-cell count of 9800, with a normal differential. The serum calcium was 12.4 to 12.8 mg, inorganic phosphorus 5.5 to 6.6 mg, nonprotein nitrogen 90 mg and alkaline phosphatase 7.2 Bodansky units per 100 cc. The chloride was 90 to 105 milliequivalents and the carbon dioxide content 30 to 35 milliequivalents per liter, and the total protein 7.7 gm per 100 cc, with an albumin of 4.96 gm and a globulin of 2.12 gm. Gastric analysis disclosed 4 units of free and 11 units of combined hydrochloric acid.

A gastrointestinal series gave evidence of an old duodenal ulcer, probably still active, with accompanying gastritis,

trogen was 48 to 75 mg, calcium 10.6 mg, phosphorus 2.0 to 2.3 mg, and alkaline phosphatase 3.0 to 3.4 Bodansky units per 100 cc, and the carbon dioxide content was 37.3 milliequivalents and the chloride 107 milliequivalents per liter. The results of laboratory studies between November 1946, and February, 1948, are presented in Figure 1. When last seen in February, 1948, the only symptoms were those referable to an obstructing duodenal ulcer. The patient had remained on a low milk and alkali and high fluid regimen since discharge.

CASE 4 T W (J H H 204618), a 38-year-old physician, entered the hospital in July, 1940, for surgical therapy of intractable ulcer symptoms. He had had symptoms of peptic ulcer, which had begun while he was in medical school in 1928. There was then a period during which he was relatively asymptomatic until 1937, when symptoms recurred and x-ray examination demonstrated a duodenal ulcer. From this time until admission he took 6 or more teaspoonfuls of sodium bicarbonate and drank 2 or 3 quarts of milk daily. Two years prior to admission nocturia and polyuria had begun and had been increasing. He had never had symptoms of nephrolithiasis.

Physical examination showed normal fundi, with conjunctival crystals and band keratopathy bilaterally. The blood pressure was 140/80.

Routine urinalysis was entirely negative. The urea clearance was 16 per cent of normal. The phenolsulfonephthalein excretion was 8 per cent in the first 1/2 hour, and 28 per cent in 2 hours. The serum nonprotein nitrogen was 78 mg, calcium 12.5 and 12.7 mg, phosphorus 6.5 and 7.3 mg, and protein 6.5 and 6.8 gm per 100 cc, and the carbon dioxide combining power was 26.8 milliequivalents, and the chloride 100 milliequivalents per liter.

A gastrointestinal series demonstrated a duodenal defect characteristic of ulcer.

Parathyroid exploration was carried out on July 10, and enlargement of all four parathyroid glands was found. Three glands and about three quarters of the remaining one were removed. The pathological diagnosis was hyperplasia of the chief and oxyphil types. On July 24 hypercalcemia was still present, the blood calcium determination being 13.5 mg per 100 cc. The serum phosphorus was 5.9 mg per 100 cc.

An exploration for parathyroid adenoma was carried out. Three parathyroid glands were located, which on biopsy proved to be normal.

During the next 2 years the patient again remained on a low calcium intake and took no alkali. He re-entered the hospital in June, 1942, because of bleeding from the duodenal ulcer. Laboratory studies were essentially the same as those on previous admissions, with the addition of a serum sodium of 135 milliequiv per liter. A plain x-ray film of the abdomen showed small kidneys and areas of calcification in the lower pole of the left kidney.

The fifth admission, in October, 1943, was for another episode of bleeding from the ulcer. Urinalysis demonstrated a +++ test for albumin. The serum calcium was 10.1 mg, the phosphorus 10 mg, and the total protein 8.6 gm per 100 cc, the chloride was 71.7 milliequiv, and the carbon dioxide content 25.6 milliequiv per liter. X-ray films of the bones were normal.

The final admission was in April, 1944, terminating in death from renal insufficiency. Laboratory studies performed shortly before death revealed a serum calcium of 7.7 mg and a phosphorus of 9.4 mg per 100 cc, a phosphatase of

There had been no urinary symptoms except nocturia, (twice) for about 2 years. Urinalysis 20 months before admission had shown a slight trace of albumin.

Physical examination revealed a very emaciated young man with marked atrophy of the skin and muscles. The eyes were prominent, and the corneas demonstrated changes consistent with band keratopathy. The fundi were normal. The skin was dry and scaly, with brownish pigmentation over some of the keratotic areas. The blood pressure was 88/70.

Routine urinalysis disclosed a maximal specific gravity of 1.008 and a +++ test for albumin, with a pH 6.5 to 7.5. The sediment contained white cells, frequently in clumps, and occasional granular casts. Urine cultures showed a moderate growth of *Staphylococcus aureus* and colon bacilli in one, and no growth in another. Phenolsulfonephthalein excretion was 3 per cent in 1 hour. The Sulkowitch test demonstrated no calcium. A test for Bence-Jones protein was negative. The urinary 17-ketosteroid excretion was 27 and 3.0 mg per 24 hours.

Examination of the blood revealed a red-cell count of 2,250,000 with a hemoglobin of 45 per cent, and a white-cell count

LOW CALCIUM, PHOSPHORUS, and ALKALI INTAKE

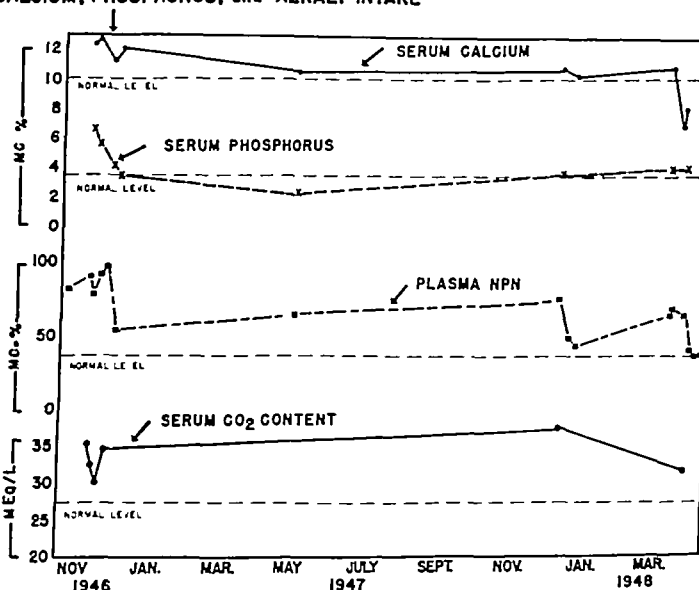


FIGURE 1 Laboratory Findings in Case 3

18.0 Bodansky units and a chloride of 84 milliequiv, a sodium of 128 milliequiv and a carbon dioxide content of 9.5 milliequiv per liter. The nonprotein nitrogen was 150 mg and the total protein 7.87 gm per 100 cc, with 5.17 gm of albumin and 2.70 gm of globulin.

The diagnoses at autopsy were as follows: chronic pyelonephritis, nephrocalcinosis, calcification of the dura mater, diaphragm, costal cartilages, tendons and blood vessels, bronchopneumonia of all lobes, gastric ulcer, well healed, and prostatic abscess. No parathyroid glands were found, but it is not known whether a careful search for them was made.

CASE 2 A C (M G H 267258), a 25-year-old man, first entered the hospital in September, 1940, complaining of vomiting and eructations for 2 1/2 years. Epigastric pain relieved by food and soda had started while he was a senior in college and worrying about examinations. A milk and alkali regimen was prescribed, and until his admission, because of persistent gastrointestinal symptoms, he was almost constantly on such a program. He had lost 50 pounds since the onset of his illness. Repeated x-ray films of the gastrointestinal tract were reported to have shown no abnormalities.

of 8500, with a normal differential. There was marked variation in the size and shape of the erythrocytes. The serum calcium was 12.0 to 12.8 mg, the alkaline phosphatase 2.8 to 6.8 Bodansky units, the protein 7.1 gm, the nonprotein nitrogen 85 mg, the cholesterol 184 mg, and the fasting blood sugar 83 mg per 100 cc. The carbon dioxide combining power was 23.3 to 30.2 milliequiv, and the chloride 89 to 95 milliequiv per liter. The basal metabolic rate was -6 per cent. In the sternal bone marrow there was no evidence of leukemia or multiple myeloma.

A gastrointestinal series gave no evidence of disease. X-ray films of the long bones showed extensive periosteal new bone formation about the humeri, radii, metacarpals, pelvis, femora, tibiae, fibulae, tarsals, and metatarsals. Films of the skull demonstrated extensive calcification of the tentorium, the falx and the dura over the cerebral hemispheres. In the chest there was extensive calcification of the bronchial tree. On a plain film of the abdomen, the kidneys were poorly outlined but appeared smaller than normal, without unusual areas of calcification within them.

On a low calcium diet the serum calcium fell to 11.2 mg, and the nonprotein nitrogen to 40 mg per 100 cc, the phosphorus, chloride and carbon dioxide combining power did

with 3.11 gm of albumin and 1.54 gm of globulin, the calcium 10.9 mg, the phosphorus 2.7 mg, and the alkaline phosphatase 3.66 Bodansky units per 100 cc. The carbon dioxide content was 29 milliequiv, the chloride 103 milliequiv, the sodium 135 milliequiv, and the potassium 4.1 milliequiv per liter.

In June a posterior gastroenterostomy was performed because of recurrent pyloric obstruction. The patient withstood the operation well. Laboratory studies shortly before discharge disclosed a serum nonprotein nitrogen of 71 mg, calcium of 9.1 mg, and phosphorus of 2.7 mg per 100 cc, with a carbon dioxide content of 29 milliequiv and a chloride of 96 milliequiv per liter.

He has remained relatively asymptomatic since discharge.

CLINICAL FEATURES

The clinical features of these cases are shown in Table 2 and 3. All 6 patients gave a similar history of having suffered symptoms characteristic of peptic ulcer for many years, in excess of ten years with the exception of 1 patient (Case 2), who had had symptoms for only two years. In 4 cases duodenal ulcer was demonstrated by x-ray examination, in a fifth (Case 5) the presence of a peptic ulcer seems almost certain although the diagnosis was never definitely established by x-ray study.

Treatment of each patient had consisted of almost continuous ingestion of large quantities of milk and absorbable alkalis, usually sodium bicarbonate, for periods of a few to many years. Nephrolithiasis had occurred in 1 case several years previously (Case 1). In 2 patients (Cases 5 and

with hypercalcemia from any cause, and have been described in a previous report,¹² which includes Cases 1, 2, 3 and 4 in this series. Cases 1, 2, 3, 5 and 6 will also be included in another report now in press.¹³ In brief, these changes are of two types. In one there are corneal changes consisting of hazy, granular and subepithelial deposits running con-

TABLE 2 Summary of Clinical and X-Ray Features

FEATURES	NO OF CASES
Ulcer symptoms for two to thirty years	6
Excessive milk and alkali intake	6
Ocular lesions	6
Renal insufficiency	6
Hypertension	5
Duodenal ulcer by x-ray study	4
Pruritus	4

centrically with the limbus on either the nasal or the temporal side or both. These lesions are similar to band keratitis, but in the opinion of Cogan¹³ are not a true keratitis and are better designated as band keratopathy. In the other type of lesion there are small glass-like particles in the conjunctivas of the palpebral-fissure area. Biopsy of this type of lesion in 1 of the cases in the series of Walsh and Howard¹² showed an amorphous material, pre-

TABLE 3 Abnormalities of Soft Tissues and Bones

CASE No.	EYES		OTHER SOFT TISSUES	BONES
	BAND KERATOPATHY	CONJUNCTIVAL CRYSTALS		
1	—	0	Nephrocalcinosis; calcification of dura mater, diaphragm, costal cartilages, tendons and blood vessels.*	Normal
2	—	0	Extensive calcification of tentorium, falx and dura over cerebral hemispheres and bronchial tree	Extensive periosteal new bone formation of long bones
3	—	0	Calcification of abdominal blood vessels	Normal
4	—	—	—	Normal
5	—	†	Subcutaneous calcified nodules of elbows † hands and knees; calcification in lung	Dense cortical bone†
6	—	0	Calcified mesenteric lymph nodes	Normal

*Autopsy

†Biopsy

6), there was a history of previous hypertension. In no case was there a history suggestive of preceding acute glomerulonephritis or pyelonephritis.

The primary complaints were exacerbation of ulcer or gastrointestinal symptoms in 4 cases, intractable pruritus in 1 and arthritic complaints in 1. Pruritus was an important secondary complaint in 3 others.

A moderate hypertension was present initially in 5 patients, and as the disease progressed, the physical findings usually became the expected ones of hypertension and renal failure.

Early in the course, the physical finding that was most striking and the only one common to all patients was that found in the eyes (Table 3^{12, 14}). The ocular lesions were believed to be associated

sumably a calcium salt beneath the conjunctival membrane. In all patients in the present series, band keratopathy was demonstrated, in 2 the conjunctival lesions were also present.

The combination of elevated serum calcium and a slightly elevated or normal serum phosphorus present in this syndrome theoretically should favor metastatic calcification. In addition to those uniformly present in the eyes, such changes were present elsewhere in 5 of the 6 patients, but they were extremely irregular in their anatomic distribution (Table 3). They varied from widespread soft-tissue calcification (subcutaneous, lungs and falx cerebri) to a few calcified mesenteric lymph nodes.

In 2 patients significant abnormalities of the bones were demonstrated. extremely dense can-

At the next admission, on October 30, the patient felt very much better and had been carrying on an active practice. The serum calcium was 12.2 mg, and the phosphorus 4.5 mg per 100 cc. The nonprotein nitrogen had fallen to 45 mg per 100 cc. He now had a secondary anemia that had not been present on the first admission.

When next seen in March, 1942, he was improved in every respect. He had no further symptoms of ulcer, and had remained on a milk-free diet without alkalis. Nocturia had diminished from five times to two times. For 2 months he had noticed tingling in the toes if pressure were made on the posterior aspects of the thighs. Trousseau's sign was positive in 90 seconds, although Chvostek's sign was negative. These symptoms of tetany were relieved by calcium acetate. The conjunctival lesions had partially cleared.

Laboratory studies demonstrated a serum nonprotein nitrogen of 52 mg, calcium of 6.4 mg, phosphorus of 6.4 mg and protein of 6.0 gm per 100 cc. The carbon dioxide combining power was 20 milliequiv, and the chloride 107 milliequiv per liter.

The patient was seen again in 1944, when retinal hemorrhages and narrowing of the retinal arteries had developed. The blood pressure had risen to 150/100. The phenolsulfonephthalein excretion was 10 per cent in the first 30 minutes, the serum nonprotein nitrogen was 64 mg per 100 cc. The calcium and phosphorus values were unchanged. The blood showed a moderate anemia.

By October, 1946, there was marked progression of the renal disease and evidence of congestive heart failure. The blood pressure was 140/100. The nonprotein nitrogen ranged between 145 and 160 mg per 100 cc. The serum calcium was 7.5 mg, the phosphorus 7.7 mg, and the protein 5.6 gm per 100 cc.

The patient died in January, 1947, an autopsy was not performed.

CASE 5* E McD (W R V A H 12467), a 55-year-old carpenter, first entered the hospital in September, 1946. One grandmother was an American Indian.

He had had symptoms and x-ray signs suggestive of ulcer since 1930 although a definite x-ray diagnosis had never been made. Treatment had consisted almost continuously of 4 or 5 quarts of milk daily and large quantities of sodium bicarbonate. Hypertension had been noted in 1930. For 5 years he had had nocturia (once or twice,) and dribbling of urination. He had complained of aching of the ankles, knees and hips for 4 years, for 6 months the ankles and lower legs had been swollen. A prominent secondary complaint was severe generalized pruritus. He had never been given vitamin D for his arthritic complaints.

Physical examination revealed an elderly appearing man whose skin was dark brown. Dime-sized, movable, firm, subcutaneous nodules were noted on the extensor surface of the forearms. Examination of the eyes disclosed white plaques on the conjunctivas and crystalline opacities along the medial edge of the corneas, there was tortuosity of the vessels of the fundi and arteriovenous nicking. A Grade II systolic murmur was heard in the aortic area. Edema of the feet, ankles and lower legs was present. The prostate was enlarged. The blood pressure was 150/80.

Routine urinalyses demonstrated a maximal specific gravity of 1.011 and a +++ to ++++ test for albumin. The sediment contained occasional white cells and red cells. The phenolsulfonephthalein excretion was 5 per cent in 1 hour. Examination of the blood showed a hemoglobin of 10.0 gm and a white-cell count of 7100, with a normal differential. The serum calcium was 11 to 14 mg, the phosphorus 4.1 to 5.9 mg, the nonprotein nitrogen 89 to 100 mg, the total protein, 7.6 gm, with 4.68 gm of albumin and 2.92 gm of globulin, and the cholesterol 320 to 550 mg per 100 cc.

A gastrointestinal series was normal. X-ray films revealed cancellous bone and a very dense skull and long bones. The falx, cerebrum and soft tissues of the knees, elbows, hands and lungs were calcified. Retrograde pyelograms disclosed slight clubbing of the calyces of the kidneys.

An electrocardiogram demonstrated myocardial disease, with right bundle-branch block and auriculoventricular block, probably on the basis of arteriosclerotic heart disease.

The patient was discharged on December 7, on a low protein and low salt diet. During the next 6 months clinically his condition remained essentially unchanged, neces-

sitating three readmissions during April, May and June, of 1947, with the same general complaints. It is questionable whether during this period he adhered to his diet, and hence whether his milk and alkali intake was much reduced.

Between April and July routine urinalyses were unchanged. The urinary calcium was 77.8 and 77 mg per 24 hours. The results of renal-function studies are presented in Table 1.

Examination of the blood showed a red-cell count of 4,300,000, with a hemoglobin of 73 per cent. The serum nonprotein nitrogen was 90 to 137 mg, the calcium 10.8 to 12.8 mg, the phosphorus 4.2 to 5.4 mg, the alkaline phosphatase 3.2 to 5.9 Bodansky units, and the cholesterol 415 mg per 100 cc. The chloride was 91 to 101 milliequiv, and the carbon dioxide content 32 milliequiv per liter. A biopsy of a subcutaneous nodule demonstrated calcified material embedded in large areas of dense fibrous tissue. A bone biopsy revealed dense cortical bone of normal architecture, with granular basophilic deposit in the periphery of the Haversian canals.

From July, 1947, to June, 1948, the patient was maintained on a regimen low in milk, sodium and protein. Subjectively he was somewhat improved, but continued to complain of joint pains, weakness and pruritus. On readmission in June, 1948, the physical findings were unchanged. There was also no change in the urine or in renal function (Table 1). The serum nonprotein nitrogen was 125 mg, the calcium 10.7 mg, and the phosphorus 2.8 mg per 100 cc, the chloride was 110 milliequiv, the sodium 138 milliequiv, and the potassium 4.3 milliequiv per liter. The protein was 7.2 gm per 100 cc, with 4.39 gm of albumin and 2.81 gm of globulin.

He was not seen again in the hospital and died at home in December, 1948. The nature of his terminal illness is unknown. Permission for autopsy was not obtained.

CASE 6 M J L (E M H 329,496), a 54-year-old fireman, was admitted to the hospital in January, 1948, because of hematemesis. Ulcer symptoms had been present for over 30 years, and treatment had almost always included several quarts of milk daily and large quantities of sodium bicarbonate. In November, 1946, the diagnoses of active duodenal ulcer and chronic nephritis had been made at the Massachusetts General Hospital.

The past history revealed a heavy alcoholic intake. Nocturia (up to five times) had been present for 5 years, and mild pruritus for 2 years. The right eye had been removed at the Massachusetts Eye and Ear Infirmary in 1945 because of changes secondary to glaucoma and chorioretinal degeneration.

The blood pressure was 130/70 after the initial hypotension due to blood loss had been relieved. The left cornea showed band keratopathy, the fundus was normal.

Routine urinalyses demonstrated a maximal specific gravity of 1.016, no albumin and a normal sediment. The results of renal-function studies are presented in Table 1. The hemoglobin was 10 gm per 100 cc. The white-cell count and differential were normal. The stools were guaiac positive during the 1st week of hospitalization. On admission the nonprotein nitrogen was 131 mg, the calcium 11.5 mg, the phosphorus 4.6 mg, and the alkaline phosphatase 4.4 Bodansky units per 100 cc, and the carbon dioxide content was 33 milliequiv, and the chloride 95 milliequiv per liter.

A gastrointestinal series revealed a duodenal defect consistent with peptic ulcer. An x-ray film of the abdomen disclosed an area of irregular density at the level of the fourth lumbar vertebra, probably representing calcified mesenteric nodes.

The bleeding stopped spontaneously, and the pyloric obstruction was treated with gastric suction. While the patient was on suction considerable alkalosis developed, with a serum carbon dioxide content of 38 milliequiv per liter and a chloride of 89 milliequiv per liter. After relief of the obstruction and parenteral administration of physiologic saline solution and the serum carbon dioxide content fell to 27 milliequiv, and the serum chloride rose to 106 milliequiv per liter, and the serum nonprotein nitrogen stabilized at 60 to 80 mg per 100 cc. He was discharged on a low milk and alkali regimen considerably improved.

In March, 1948, he was readmitted for further renal-function studies. Physical examination was unchanged. Examination of the urine was also unchanged. The results of renal-function tests are presented in Table 1. The serum nonprotein nitrogen was 62 mg, the total protein 4.64 gm,

*We are indebted to Dr A. S. Zdanis for asking us to study this patient.

explanation because of certain atypical features of the syndrome, no one of which is insurmountable but which taken as a group could hardly be explained by primary hyperparathyroidism. These features are lack of hypophosphatemia accompanying the hypercalcemia, lack of hypercalcuria, lowering of the serum calcium on a low calcium intake, and absence of skeletal demineralization or its laboratory manifestation, elevation of serum alkaline phosphatase.

Renal failure associated with hypercalcemia in diseases other than hyperparathyroidism has been observed in acute osteoporosis,¹ hypervitaminosis D,²⁻⁴ sarcoidosis,⁵ myelomatosis,⁶⁻⁸ and generalized carcinomatosis with metastatic bone involvement.⁶ All these conditions seem to have been adequately excluded in this series. A special search was made in each case for a history of excessive intake of vitamin D, none was elicited.

In chronic Bright's disease with uremia, there are usually hypocalcemia, hyperphosphatemia and metabolic acidosis,¹⁶⁻¹⁸ a very different biochemical pattern from that described above.

The possibility that ulcer regimens employing milk and absorbable alkalis adversely affect kidney function has been suggested repeatedly. There is little question that acute alkalosis may cause a temporary and sometimes marked diminution in renal function, and that a subsequent striking improvement may occur after correction of the alkalosis.¹⁹⁻²² Some observers have found no evidence of antecedent renal disease in their patients.²³⁻²⁴ Definite proof that alkalosis can cause any permanent renal damage is still lacking.²¹⁻²²

The present series of cases is somewhat different from previously reported ones, in that no episodes of acute alkalosis with accompanying severe dehydration, hypochloremia and azotemia were known to have occurred. All patients were found to be suffering from chronic renal failure, usually incidental to other complaints. In the 2 patients who are still living and in the 3 who died on whom autopsies were not obtained, the histories gave no evidence of previous renal disease, although 2 were known to have had hypertension. The case in which a post-mortem examination was performed showed a renal lesion diagnosed as pyelonephritis and nephrocalcinosis. From this case alone, one might hypothesize that for the production of the syndrome the presence of underlying renal disease is necessary, on which is superimposed the harmful effect of milk and alkalis on the kidneys. On the other hand in Case 2 urinalyses were normal, as was a kidney biopsy only two years before renal insufficiency developed, so that there is little evidence of antecedent kidney disease in this case. The final answer clearly must await more extensive observations.

The abnormalities of calcium metabolism as evidenced by calcinosis and hypercalcemia are extremely puzzling, and no complete explanation

for them is evident from our data. Hypercalcemia has previously been observed during episodes of acute alkalosis associated with excessive intake of alkalis and calcium.²⁴⁻²⁵ To our knowledge cases of prolonged hypercalcemia and renal failure such as those observed in this series have not been recorded. The absence of hypercalcuria and the lowering of the serum calcium level following low calcium intake suggest an interference with the renal excretion of calcium. The exact mechanism of this interference with excretion cannot even be speculated upon until the normal mechanisms for the renal excretion of calcium are elucidated.

The mechanism of a slight persistent alkalosis after relief of vomiting and withdrawal of alkali is equally difficult to explain. There may have been, of course, vomiting or alkali ingestion of which we were unaware when the high serum carbon dioxide contents were observed, but this explanation seems unlikely. When serum sodium determinations were done they were normal or slightly low, and the alkalosis was not invariably accompanied by hypochloremia. The association of intracellular potassium deficiency and alkalosis suggests itself.²⁶⁻²⁸ However, there is no reason to believe that there was such a deficiency in any of these patients, and the serum potassiums when measured were normal.

The observation of high serum proteins with the elevation chiefly in the albumin fraction is also most unusual. They were determined in several different laboratories, by the usual Howe technic, and appear consistent enough to exclude artifacts or errors in measurement.

Each of these patients showed evidence of improvement after institution of low milk, low alkali and high fluid intakes. Subjectively they felt better, chemically, the azotemia diminished in all patients, and hypercalcemia diminished in the 5 cases in which it was demonstrated. This therapeutic response strengthens our conviction that the deranged homeostasis was in some manner associated with the excessive ingestion of milk and alkalis.

SUMMARY

A syndrome observed in 6 male patients, all of whom gave the common history of peptic ulcer or ulcer symptoms treated by excessive intake of milk and alkalis for many years, is described.

The syndrome is characterized by a history of prolonged and excessive intake of milk and absorbable alkali, hypercalcemia without hypercalcuria or hypophosphatemia, normal serum alkaline phosphatase levels, marked renal insufficiency with azotemia, mild alkalosis, calcinosis manifested especially by an ocular lesion resembling band keratitis, and improvement on an intake low in milk and absorbable alkali.

Although primary hyperparathyroidism could not be excluded positively in all patients, the evi-

cellous bone in Case 5, and extensive periosteal new bone formation in Case 2. The bones in the remaining 4 cases were normal.

Four patients have died, the other 2, although they still show evidence of renal insufficiency, remain symptomatically improved.

LABORATORY FINDINGS

The laboratory findings are summarized in Table 1 and 4. The biochemical abnormalities in the blood and urine were usually unsuspected and always puzzling. In general they were at first inspection those of advanced renal insufficiency,

TABLE 4 Summary of Laboratory Findings

FINDING	No. OF CASES
Renal insufficiency	6
Azotemia	
Fixed urinary specific gravity	
Depression of renal function tests	
Hypercalcemia	5
No hypercalcuria	5
Mild alkalosis	5
Albuminuria	3

but with definite differences from the pattern usually seen in uremia.

Azotemia was always present, the nonprotein nitrogen level varied from 50 to 150 mg per 100 cc. Under treatment the nitrogen retention usually diminished.

Definite hypercalcemia was present in 5 patients, the serum calcium level varying between 12.0 and 14.5 mg per 100 cc. In Case 6 only a moderate hypercalcemia was demonstrated (11.2 mg per 100 cc) after the patient came under observation. However, in several of the other patients, the serum calcium fell as renal failure progressed. We have assumed that a more severe hypercalcemia had been present in the past in this patient since he showed all the other characteristics of the syndrome.

The serum phosphorus typically was normal or high, varying from 3.0 to 7 mg per 100 cc. Except for a terminal level of 10 mg in Case 1, none of the patients ever exhibited the degree of hyperphosphatemia usually present in uremia, nor was the hypophosphatemia of hyperparathyroidism present at the time when the serum calcium was elevated. Another puzzling feature of the syndrome is the fall in serum phosphorus in some cases after withdrawal of milk and alkali. Thus, in Cases 3 and 5, although the serum calcium levels fell from 12.8 and 14 to 10.6 and 10.7 mg per 100 cc respectively, the serum phosphorus levels fell from 6.6 and 5.9 to 2.0 and 2.6 mg per 100 cc respectively. In Case 5 (in which only moderate hypercalcemia was demonstrated), the serum calcium levels remained at 11.5 and 10.9 mg per 100 cc, whereas the serum phosphorus levels fell from 4.6 to 2.7

mg per 100 cc. It appears that the high phosphate, as well as the high calcium content, of milk is a factor in this syndrome.

Urinary calcium excretion was not shown to be increased by quantitative measurements in 3 patients or by the Sulkowitch test in 2.

Instead of the acidosis (as evidenced by low serum carbon dioxide content) usually seen in renal insufficiency, 5 patients had at some time slightly high carbon dioxide contents of the serum, ranging from 30 to 36 milliequiv per liter. At times this was associated with alkali ingestion and vomiting, but the tendency toward alkalosis occasionally persisted so far as could be determined even after these factors had been removed. In 1 fatal case (Case 1) acidosis eventually developed during the terminal phase of the illness.

The serum protein levels were not so low as might have been expected in view of the degree of renal insufficiency present, indeed, in 3 patients (Cases 1, 3 and 5) actual hyperproteinemia was demonstrated. On fractionation this elevation appeared to be chiefly in the albumin in each case.

Albuminuria was present in all but 1 patient. The urinary sediment contained no abnormal constituents in 2 patients, in the other 4 it contained occasional to rare hyaline and granular casts, infrequent red cells and occasional to many white cells. Urine cultures were negative in 1 patient, grew *Staph aureus* and *Esch coli* in 1 and *Staph aureus* and *albus* in 1, and were not done in 3 patients.

The results of the various renal-function measurements, which are presented in Table 1, indicated advanced renal disease. Ability to concentrate the urine was uniformly absent. From the renal clearances in 3 patients it is apparent that all portions of the nephron were impaired. The high filtration fraction and the high ratio of glomerular filtration rate to maximal tubular excretory capacity suggest relatively greater insufficiency of tubular as compared with glomerular function. The recognized limitations of clearance technics in advanced renal disease, however, render such a conclusion only tentative.

DISCUSSION

The presence of primary hyperparathyroidism was suspected in each of these cases. In 1 patient who died the parathyroid glands were not located at autopsy. This is the same patient (Case 1) in whom three years previously normal parathyroid glands had been found at operation. One other patient (Case 4) who was explored showed parathyroid hyperplasia of the chief and oxyphil cell variety thought to be characteristic of secondary hyperparathyroidism.¹⁵ In the other 4 patients it is admittedly impossible to state that primary hyperparathyroidism was not present in addition to renal failure. We have been led to seek another

least 7 gm of solid potassium permanganate, the post-mortem findings and subsequent investigations are judged to have been of sufficient interest to warrant presentation

CASE REPORT

A 21-year-old single woman, pregnant for the second time, entered a general hospital in a state of acute collapse with slight to moderate vaginal bleeding and brownish staining of the perineum. Death occurred about 8 hours later. The total duration of illness was said to have been about 12 hours. The history given by her sister, a nurse, was that the decedent had attempted abortion by douching herself with a solution of potassium permanganate. This solution is said to have been prepared by the addition of about 2 ounces of permanganate crystals to 3 ounces of water.*

Post-mortem examination, conducted 6 hours after death, showed the body of a well developed and well nourished woman of about the stated age. The entire skin surface was a uniform, light-mahogany brown, although prior to the fatal illness, it was learned, the skin had appeared a normal white. The uterus could be palpated as a soft freely movable intra-abdominal mass extending from the pubis almost to the umbilicus. There was focal and confluent superficial hemorrhagic necrosis of intravaginal cervical epithelium, and a small amount of liquid blood oozed from the dilated cervical canal.

On internal examination the principal abnormalities were to be found in the soft and boggy uterus, which measured 18 by 14 by 10 cm and showed a diffusely hyperemic serosal surface. The cervix was soft and flattened in its inferior-superior aspect. The os was dilated to about 1.0 cm in diameter. Upon opening, the inner aspect of the uterus showed diffuse superficial hemorrhagic necrosis, the cavity contain-

ing masses of purplish-red coagulum. No definite evidence of fetal components could be identified grossly.

The other organs showed nonspecific changes, principally hyperemia. There was no evidence of exsanguination. On microscopical examination of the uterus the disorganized remnants of a decidual reaction could be identified in the decidua and in the poorly staining superficial myometrium.

*A saturated solution of potassium permanganate contains 6.38 gm. per 100 cc. at 20 C. How much if any, of the undissolved permanganate was carried along in the process of injecting the solution could not be determined.



FIGURE 1 Exudative Reaction in a Dilated Vessel of a Superficial Section of the Cervix (Hematoxylin and Eosin Stain $\times 200$)

The superficial cervical stroma contained foci of hemorrhage. There was a marked perivascular and intraluminal (Fig. 1) accumulation of exudative cells, mostly polymorphonuclear leukocytes, in the vessels in this location. This irritative re-



FIGURE 2 Pigment Casts in Lower Portions of the Nephron (P.T.A.H. Stain $\times 50$)

action was much more prominent than it was in comparable areas in the uterus. Although the kidneys grossly were not regarded as showing significant changes, microscopical examination revealed the presence of numerous pigmented casts, chiefly in the lumen of the tubules designated as "lower nephron" (Fig. 2). The vasa recta were engorged. There was no significant alteration of the tubular epithelium. None of the other viscera showed changes of note except for hyperemia and moderately severe pulmonary edema.

dence, in our opinion, suggests that the abnormalities observed in the calcium and phosphorus metabolisms were a result of the following sequence of events excessive intakes of milk (a foodstuff high in calcium and phosphorus) and alkalis, kidney damage, tendency to fixation in urinary calcium excretion, hypercalcemia, tendency to supersaturation in respect to calcium phosphate, and calcinosis. The improvement resulting from a low intake strongly supports this sequence.

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DEATH FROM ATTEMPTED ABORTION WITH A POTASSIUM PERMANGANATE DOUCHE

WALTER W. JETTER, M.D.* AND FRANCIS T. HUNTER, M.D.†

BOSTON

ALTHOUGH potassium permanganate is commonly employed as a disinfectant and deodorant and for local application in the treatment of dermatitis, fatal poisoning from its use is rare. As evidence of this, Green and Warr,¹ in reviewing the literature from 1899-1941, were able to find only 8 fatal cases. On the other hand, these authors reported 31 cases in which potassium permanganate was ingested, none of which resulted fatally. Except in children, the poison was invariably swallowed with suicidal intent, since the intense blue color of even a very dilute solution tends to make disguise difficult.

Within recent years, necrotizing injury of the vagina and cervix due to the use of potassium permanganate tablets (0.3 to 1.0 gm.) as an abortifacient has been reported in increasing numbers of cases, mostly from European countries.²⁻¹⁴ That the practice occurs also in this country has been stressed by McDonough,¹⁵ who reviewed 65 cases,

in all of which admission of the use of potassium permanganate as an abortifacient was sooner or later obtained from the patient. Actually, only 6 patients were successful in the attempt to terminate the pregnancy. The chief clinical evidence was bleeding, which usually occurred within two hours of the insertion of the tablet. Although none of the cases reported by McDonough ended fatally, operative intervention by suturing at bleeding sites was necessary in 10 cases, and in 34 others close packing of the vagina for forty-eight hours was necessary to control the hemorrhage. Twelve patients required treatment for shock, with multiple transfusions. There was no evidence of toxemia that was thought to be attributable to systemic absorption of the chemical itself.

The case presented below is the first to our knowledge in which death has occurred after the use of potassium permanganate as an abortifacient. Although the circumstances are unusual in that the abortive procedure consisted in the intravaginal instillation of what was apparently a saturated solution of potassium permanganate containing at

*Assistant professor of legal medicine, Harvard Medical School, pathologist, Massachusetts Department of Mental Health.

†Associate in medicine, Harvard Medical School, associate physician and clinical pathologist, Massachusetts General Hospital.

reveal the form in which manganese was distributed systemically, it seems highly probable that the compound present in the tissues post mortem was a reduction product of permanganate. This does not necessarily imply that the permanganate molecule as such did not enter the blood vessels during life. Certainly, the local environment was favorable for permanganate to enter the uterine circulation through the widely dilated sinusoidal channels of the richly vascular decidual tissue. Since potassium permanganate acts so quickly, hemolysis may have taken place in the small uterine sinusoids before this blood moved on into the venous circulation.

Apparently, it has not been generally appreciated that permanganate may act as an acute hemolytic agent, although the hemolytic effect of a somewhat similar oxidizing agent, potassium chlorate, is well known. Homma¹⁹ states that permanganate causes methemoglobin formation *in vitro* but not *in vivo*. Palmieri,²⁰ in a fatal case caused by the suicidal ingestion of about 25 gm of potassium permanganate, could not demonstrate methemoglobin in the post-mortem blood*. However, photomicrographs of the kidney of this case showed pigment in the lumen of collecting tubules resembling that seen in the case reported above. Concerning the presence of pigment casts in the kidney, it is probable that our patient would have developed the syndrome of lower-nephron nephrosis had she lived sufficiently long.

The formation of abnormal blood pigments *in vivo* can be brought about in a number of ways, but the particular hemoglobin derivative produced depends on mechanisms not yet well understood. Many chemicals, particularly the aromatic amino and nitro compounds, have the capacity of converting intracellular hemoglobin to methemoglobin without necessarily causing hemolysis. The spectrum of such a blood laked with distilled water *in vitro* shows methemoglobin chiefly in the "neutral" form. On the other hand, intravascular hemolysis may or may not cause the formation of methemoglobin. As examples, a patient recently seen with blackwater fever showed a large amount of "neutral" methemoglobin in the serum whereas in 12 cases of intravascular hemolysis due to the entrance of water into the circulation, not one showed evidence of methemoglobin in the serum; instead, the serum pigments consisted of oxyhemoglobin, alkaline hematin and bilirubin in varying proportions.²¹

The production of methemoglobin by permanganate, however, differs from the foregoing in that both hemolysis and pigment formation are caused by a strong oxidizing agent. With rupture of the red cell, the hemoglobin is freed and is instantly oxidized to methemoglobin. But since the amounts of permanganate used in the animal experiments increased the serum pH to only a slight extent

(maximum, 7.65), it is difficult to see just why such a large proportion of the methemoglobin thus formed was in the alkaline form.

In addition to intravascular hemolysis, other types of systemic intoxication potentially may occur in acute permanganate poisoning. The first of these is hyperkalemia. An increase in plasma potassium may have occurred in two ways in our case

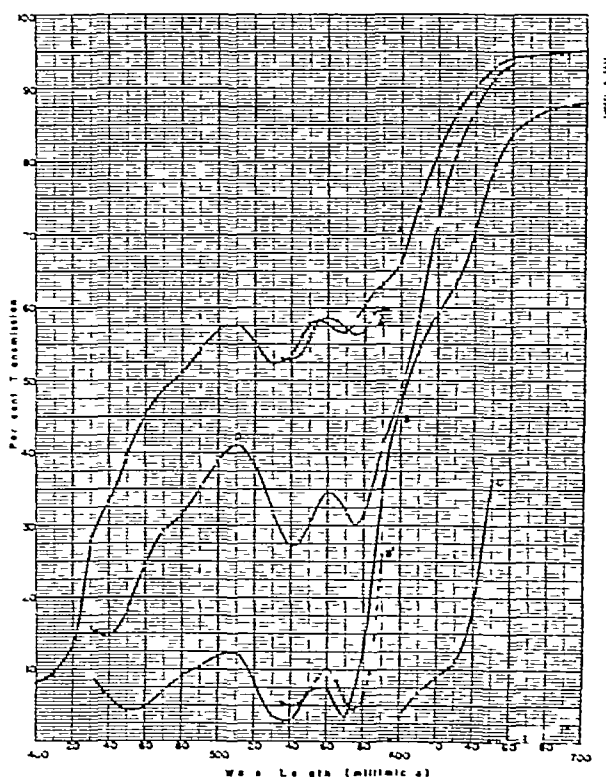


FIGURE 3. Spectrophotometric Transmittance Curves. A, B and C represent serum from a rabbit injected intravenously with 50 cc of 10 per cent potassium permanganate and killed half an hour later, diluted respectively 1:21 with 0.1 per cent sodium carbonate, 1:5 with water and undiluted (wave-band width, 14.0 millimicrons). A and B demonstrate corresponding curves with a wave-band width of 4.5 millimicrons. D shows pure methemoglobin, 72.5 mg per 100 cc, at a pH of 10.7.

by absorption of potassium ions after breakdown of the permanganate molecule in the reproductive canal, and by the release of potassium incident to intravascular hemolysis. Although it is entirely possible that hyperkalemia contributed to death, we have no objective chemical or other evidence of this. Potassium determinations in post-mortem plasma are unreliable in predicting the ante-mortem level because of the progressive increase in the potassium ion taking place after death.²²

A second possible cause of systemic poisoning is the reduction product, manganese dioxide. Local absorption of this substance is highly limited because of its insolubility. Parenteral administration

*The author demonstrated sulfhemoglobin which is often present in blood after death.

For spectrographic examination for manganese* a specimen of heart blood and about half the uterus were submitted. Samples of these were separately ashed at low temperatures, and the resulting ashes were separately examined on the spectrograph. Manganese was detected in both the specimens, but the spectral lines of manganese from the uterus sample were more intense than those from the blood. A control specimen of normal blood showed very faint lines of the manganese spectrum, evidently representing the small trace of manganese normally present in this material.

The heart blood was fluid and dark purple. On exposure to air it turned to what appeared to be the usual normal red. Upon centrifuging, however, the serum was medium brown. The intensity of the color was far in excess of that which could possibly be accounted for by the presence of manganese dioxide alone. It was decided, therefore, to investigate this pigment further. With a visual (Zeiss) spectroscope, the serum specimen showed two absorption bands of about the same width, — but without sharp margins, — at 540 and 575 millimicrons. These observations were regarded as indicative of the presence of either oxyhemoglobin or alkaline methemoglobin, more likely the latter. The addition of strong sodium hydroxide and a crystal of sodium hydrosulfite (lykopen) produced characteristic bands at 535 and 560 millimicrons of hemochromogen — indicating that the pigment was a hemoglobin derivative. To establish definitely the nature of this pigment the following experiments were carried out.

In Vitro Experiments

To 10 cc of heparinized normal whole human blood, 0.2 cc of 10 per cent potassium permanganate was added. After centrifugalization, the plasma showed a deep brown color, and on comparison with an untreated specimen of the same blood, the hematocrit value was reduced from 44 to 35 per cent, indicating a hemolysis of approximately 20 per cent.

To normal human blood diluted and laked with distilled water, a drop of dilute potassium permanganate was added. This instantaneously converted the oxyhemoglobin to a brownish-red pigment, showing absorption bands at 540 and 575 millimicrons, *similar in all respects to those observed in the serum of the decedent*. Moreover, in a concentrated solution, a faint but definite absorption band was seen at 630 millimicrons. Upon reduction with crystalline sodium hydrosulfite (lykopen), this pigment was converted to reduced hemoglobin. These observations were explicable only if the brownish-red pigment were alkaline methemoglobin with merely a trace of the "neutral" form. Since methemoglobin in aqueous solution behaves as an indicator, both forms (neutral and alkaline) are present in varying proportions at pH values between 5 and 10. That the pigment was *not* hematin was shown by its reduction to reduced hemoglobin rather than to hemochromogen.

In Vivo Experiments

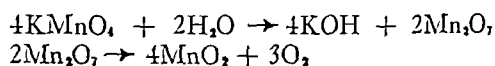
Rabbits were injected via the ear veins with a 1 per cent solution of potassium permanganate in amounts ranging from 1 to 5 cc. Immediately after injection the ear veins were outlined by a brownish discoloration, and in the animals allowed to survive, these veins became thrombosed and ischemic necrosis resulted. After injection there was an initial short period of minor collapse, but with this exception the clinical course of these animals was uneventful. In 2 animals killed at the end of 1 and 2 weeks there was no evidence of pathologic change. The kidneys of animals killed 24 hours after injection, however, showed pigment casts in the lumens of many tubules.

Serum was obtained from animals killed at periods ranging from 30 minutes to 2 days after injection. In all cases, alkaline methemoglobin was the principal abnormal pigment present. Continuous transmission curves made in the spectral region between 400 and 700 millimicrons showed the presence of alkaline methemoglobin, with only a trace of methemoglobin in "neutral" form. These curves are demonstrated in Figure 3. The steep rise of the transmission curves as they approach the longer wave lengths and the bands at 540 and 575 millimicrons are produced by alkaline methemoglobin. However, the slight "plateau" at 630 millimicrons is caused by the neutral form of the pigment. Although the pH of the serum in all cases was

considerably below 8.0, spectrophotometric quantitation showed over 90 per cent of the pigment to be in the alkaline form. At present no explanation of this observation can be offered.

DISCUSSION

Potassium permanganate is a strong oxidizing agent reacting promptly with protoplasm and most organic material, and at the same time undergoing reduction to the brown, almost completely insoluble oxides of manganese. Brown staining of tissues due to the formation of this oxide at sites of reaction may be regarded as pathognomonic of the injury produced by permanganate. Since the interreaction of the chemical and tissue is so prompt, the local necrotizing effect of permanganate is initially confined superficially to the site of surface contact. Further corrosive injury due to the formation of potassium hydroxide may take place, however, assuming that the reaction given below is a representative one.



A characteristic of a strong alkali is to penetrate into deeper tissues, leading to progressive injury. Death in the case reported above probably occurred too soon for significant manifestations of potassium hydroxide penetration to take place. Two fatal cases of permanganate poisoning cited in the literature, however, may demonstrate the occurrence of deep-seated damage by secondarily formed potassium hydroxide. In 1 case¹⁶ death occurred several days after permanganate ingestion from erosion of a gastric vessel and subsequent fatal acute hemorrhage. In the other,¹⁷ after intra-urethral instillation of 200 cc of 10 per cent potassium permanganate solution, perforation of the urinary bladder occurred and finally death from peritonitis. In some of the nonfatal cases described by McDonough,¹⁵ scar-tissue deformation of vagina and cervix occurring as late complications are more easily explained by the deep-seated injury due to potassium hydroxide than they are by the more superficial injury caused by the permanganate molecule per se.

After ingestion, the clinical features of permanganate poisoning are those of local corrosive injury. The occurrence of secondary shock when sufficiently large amounts are taken (lethal dose 10 to 20 gm)¹⁵ has usually been regarded as a nonspecific general manifestation of the severe local injury rather than as systemic toxicity of permanganate per se. By the same rationale, no different interpretation is needed to explain collapse following permanganate injury of the reproductive canal.

A critical appraisal of the case presented indicates that, in contradistinction to the conventional opinion, permanganate may act as a systemic poison. Spectrographic examination of heart blood revealed the presence of a manganese compound, suggesting that absorption had taken place. Although the spectrographic examination did not

*Performed by Lieutenant Joseph T. Walker, Ph.D., State Police Chemical Laboratory, Massachusetts Department of Public Safety.

CLINICAL NOTE

HEREDITARY MULTIPLE EXOSTOSES

JOSEPH ROSE, M D,* AND PAUL D DOOLAN, M D †

WASHINGTON, D, C, AND BOSTON, MASSACHUSETTS

HEREDITARY multiple exostoses are a distinct clinical entity more frequently encountered than is generally appreciated

We have recently had the opportunity of studying 4 members of a Negro family who had the condition. Few cases occurring in Negroes are reported in the American literature.^{1,2} To our knowledge this is the first Negro family studied and reported.

The cases were typical in both the clinical and roentgenologic aspects, varying, of course, in degree. It was our intention originally to include total protein, dextrose tolerance, calcium, phosphorus and other hormonal excretion studies in the investigation. Owing to circumstances beyond our control it was not possible to do so.

CASE REPORT

CASE 1. M C, a 40-year-old Negress, the mother of the family, demonstrated completely asymptomatic growths about the knees with genu valgus. She was unaware of them up to the time x-ray films were taken. Consanguinity was denied and no further genealogy could be elicited. The creatinine excretion was 0.96 gm, and the 17-ketosteroid excretion was 3.9 mg.† Both values were low, but their significance, if any, is unknown.

CASE 2. A C, a 19-year-old daughter, first noticed the growths about the knees when 9 years old. There was involvement of the extremities, and full extension of the forearms was not possible. The tumors progressed in size until the age of 13, after which they remained quiescent. She had some aching in the feet and ankles for a week or more after even trivial trauma, but otherwise was completely asymptomatic. A urinalysis, hemogram and blood sugar, alkaline phosphatase, serum calcium and phosphorus determinations were normal. We were unable to obtain total 24-hour urine specimens.

CASE 3. In S C, a 14-year-old son, the exostoses first appeared at the age of 6 and had continued to increase in size. There was shortening of the forearms, with lack of full extension, as well as some limitation in movement of the legs. The laboratory procedures enumerated above gave normal values.

CASE 4. In S C, a 9-year-old daughter, the protuberances were noted within the past year with seemingly no progression. There were no symptoms.

DISCUSSION

As Ehrenfried⁴ stated, the disease is a distinct clinical entity with the following characteristics: the occurrence of multiple, more or less symmetric cartilaginous and osteocartilaginous overgrowths

within and on the skeletal system, the presence of certain typical distortions and deformities of the skeleton, and the demonstration of inheritance in a large proportion of the cases. The appearance of the knees of the members of the family under discussion is shown in Figure 1.

The hereditary nature of the condition was most extensively studied by Stocks and Barrington,⁵ who reported that out of a total of 1189 cases a definite familial history was elicited in 76.5 per cent, 69.6 per cent of the patients were males. The disease probably cannot be transmitted through an unaffected male but can definitely be transmitted through an unaffected female, and the suppression



FIGURE 1 Photograph of the Family at First Examination

or latency of the disease in one generation does not involve any weakening in the power to transmit it to the next generation. The association of multiple exostoses with multiple enchondromas is more frequent in patients with a hereditary history.

Congenital exostoses and a case discovered shortly after birth have been described,⁵ but, by and large, the condition is mostly frequently detected during the periods of growth up to puberty, and few cases are reported in which the tumors appeared after the age of twenty.

There may be no signs or symptoms so that the condition is detected only on x-ray study, usually for some unrelated condition. In other cases the growths may be visible and palpable but cause no other complaints. In typical cases there are certain characteristics: shortness of stature due to defective growth of the lower extremities whereas the trunk is normal, forearm deformities, including shortening, bending and inability to extend the forearms fully (asymmetry of the extremities may be obvious), and genu valgum (scoliosis, kyphosis and

*Chief Dispensary Service, Children's Hospital, Washington, D. C.

†Medical intern, Fifth and Sixth Medical (Boston University) Services, Boston City Hospital.

‡The determinations were made in Dr. Lawrence Kyle's laboratory at Georgetown University Hospital.

leads to convulsive seizures and terminal coma in animals²³—symptoms that did not appear in the fatal case described above

SUMMARY

A case of a twenty-one-year-old pregnant woman who died approximately twelve hours after a potassium permanganate douche used as an abortifacient is presented. So far as can be ascertained, no similar case has been described.

The principal morphologic findings were extensive superficial hemorrhagic necrosis of the uterus, pigmented casts in the collecting tubules of the kidney, and evidence of acute intravascular hemolysis. The blood serum contained alkaline methemoglobin. The skin was discolored brown because of the presence of this pigment in the peripheral vascular bed.

On the basis of this case and of the experimental work reported herein, it is postulated that in acute permanganate poisoning death may be caused by one or any combination of the following processes: circulatory collapse (secondary shock) incident to severe local injury, intravascular hemolysis, hyperpotassemia due to local absorption of potassium ions, and potassium ion release incident to acute hemolysis.

Potassium permanganate in vivo and in vitro leads to lysis of red blood cells and to spontaneous conversion of released hemoglobin to methemoglobin, chiefly in the alkaline form.

Since the above report was written, another almost identical case has come under investigation in which an ante-mortem catheter specimen of urine was deep brown. The pigment showed the spectroscopic characteristics of methemoglobin, it was converted by sodium hydrosulfite to reduced hemoglobin, and then by a strong solution of sodium hydroxide to hemochromogen. This methemoglobin was chiefly in the alkaline form, and spectrophotometric quantitation showed total pigment concentration to be 16.7 gm per 100 cc.

The post-mortem blood was likewise deep brown and showed only about 10 per cent of red cells after centrifuging, and the plasma had the same appearance and gave the same reactions as the urine. Quantitated as alkaline methemoglobin, the plasma concentration was 14.9 gm per 100 cc. Since post-mortem blood samples frequently show high con-

centrations of red cells, this figure (indicating almost complete hemolysis) is not so unreasonable as it seems at first sight. Evidently hemolysis and oxidation of hemoglobin to methemoglobin continued after death.

Although it was impossible in this case to obtain information about the chemical used in the douche, potassium permanganate was doubtless employed since the spectrographic examination of uterine tissue showed definitely a larger amount of manganese than normal.

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A COMPARISON OF PTEROYLGLUTAMIC ACID AND LIVER EXTRACT MAINTENANCE THERAPY IN SPRUE*

HERBERT J. FOX, M.D.†

DURHAM, NORTH CAROLINA

THE effects of synthetic folic acid in sprue have been studied by several groups of investigators. Both Darby et al.¹ and Suarez and his associates² reported that the substance had a prompt and dramatic clinical and hematologic effect with remissions comparable or superior to that which follows liver therapy. A daily dose of 2.5 to 5 mg was considered to be adequate although in many cases the periods of observation were brief. Davidson and his co-workers,³ on the other hand, treated 10 cases of sprue with folic acid with only moderately good hematologic results, noting that macrocytosis persisted.

The present report deals with hematologic and certain clinical changes observed in 7 patients with sprue receiving maintenance dosage of synthetic folic acid for a period of at least one year. All these patients had chronic disability in spite of years of nutritional therapy, liver and vitamin supplements. This report deals with an appraisal of the comparative effects of liver and folic acid as maintenance therapy in such cases. Results of fat-balance tests and roentgenographic and biochemical studies are being presented elsewhere.

All patients were white adults native to the Carolinas, and had been under observation at this hospital for a number of years. A report on many of them has appeared in the study made by Hanes.⁴ Careful and continued follow-up observations on this group ranged from four to eighteen years, during which time they were hospitalized for treatment of sprue. All had symptoms and signs typical of the sprue syndrome: recurrent diarrhea, steatorrhea, meteorism, progressive loss of weight, glossitis, anemia and abnormal x-ray patterns of the small intestine. Two to four hospital admissions had been

required because of recurrent relapses during the preliminary time of study. The patients had all returned to the clinic at intervals of three months or less, because of a variety of complaints and disabilities.

Seven patients, 4 of whom were males and 3 females, with chronic sprue were chosen for study. Before the beginning of folic acid therapy, all of them had received prolonged treatment with low-fat diets, various vitamin preparations, and purified liver extract, dosage of 30 units to 60 units, administered parenterally once a week. These measures had failed to restore to normal the weight, stools and blood values.

Two of the patients included in this report were not having diarrhea and had not taken parenteral liver for several months. They were given folic acid because they were underweight, had abdominal distention and lacked a sense of well-being. That folic acid is beneficial in such cases can be noted in Cases 2 and 3 (Table 1).

For more than a year, these 7 patients have been closely observed while receiving synthetic folic acid,† orally as the sole specific therapeutic agent. All were rehospitalized for complete fat-metabolism studies and were examined in the clinic once a month. The dosages as well as the hematologic and clinical findings before and after treatment with folic acid are given in Table 1 and 2. The values for the white-cell count and differential formula and reticulocyte percentage were within normal limits in these cases and therefore are not included.

DISCUSSION

Hematologic Features

Table 2 shows the blood values before the start of folic acid therapy compared to the values one

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†Associate in Medicine, Department of Medicine, Duke University School of Medicine.

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talipes valgus occur, but there is no alteration in the physiognomy)

The patient may have complaints referable to joint interference or pressure phenomena on nerves or blood vessels, or the new growths may cause pain. Growths in the pelvis are a cause of dystocia.

The condition is primarily limited to the long bones, where the tumors may appear anywhere along the bone but are more frequent at the juxta-epiphyseal regions. Furthermore, it has been shown

dromas. The ends of the bones may fail to develop, giving the femur a squared-off shape. When this happens in the radius and tibia there is bowing of the adjacent bone—namely, the ulna and fibula. Synostoses of the upper end of the fibula with the tibia and fusion of the lower end of the ulna with the radius can occur. The Madelung deformity of the radius may be present.

Grossly, the exostoses are firm, lobulated tumors covered by a glistening, fibrous envelope that, on cutting, reveals a thin outermost layer of connective tissue beneath which, and appearing more prominently, is a zone of cartilage. The innermost regions are occupied by bone. Microscopically the surface envelope is seen to be composed of fibrous connective tissue, which in places blends almost imperceptibly with bone, whereas elsewhere it joins the subadjacent cartilage. The cartilage in its deeper layer becomes calcified and may either abut on spicules of laminated bone or merge into a region of cartilage removal and bone deposition. In the latter areas osteoblasts and osteoclasts may be seen. The bone is cancellous in structure, and the interspaces are occupied by fatty marrow.

Malignant degeneration is rare, being more common in cases of the single than of the multiple type.^{6,7} If neoplastic changes arise in the multiple cases they will do so from one growth so that an increase in size in a previously dormant osteochondroma should alert one to the possibility. Osteogenic sarcoma, chondrosarcoma, chondromyosarcoma and spindle-cell sarcoma are the malignant lesions that have been described. Osteogenic sarcoma arising from an exostosis is less malignant and bears a better prognosis than that of the primary type.

Many theories⁷⁻¹⁴ have been put forth in an attempt to explain the etiology. The fundamental cell in exostoses of enchondral or intramembranous origin, as well as enchondromas, is the mesenchymal cell. This cell, depending on the stage of its differentiation when stimulated as well as the duration of stimulation, can give rise to connective tissue, cartilage or bone. The stimuli that may initiate the progress are as follows: hereditary diathesis and defect in bone growth itself, growth, with its concomitant stresses and strains, metaplasia due to alteration in the physicochemical environment induced by hormonal or other metabolic factors, and trauma or infection in certain cases of single growth.

We are indebted to Dr. Charles F. Geschickter, professor of pathology, and Dr. Murray Copeland, professor of oncology, Georgetown University School of Medicine, and Dr. Donald G. McKay, assistant in pathology, Mallory Institute of Pathology, Boston City Hospital, for their help.

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FIGURE 2 Typical Roentgenologic Appearance of the Involved Bones

that the most actively growing end of the bone bears the brunt of the involvement. The growing ends of the lower-extremity bones are nearest the knee, whereas in the upper extremity they are located at the shoulder and wrist, which explains the frequency of osteochondromas around the knee and their comparative rarity near the elbows.

The characteristic roentgenologic picture is that of numerous osteochondromas in the metaphyseal region of the long bones (Fig. 2). The metaphysis is wider and somewhat longer than normal, and the cortex is thin. The exostoses vary in configuration, usually point in the direction of muscle pull and may arise from a broad base of cancellous bone or from a pedicle. There may be associated enchon-

A progressive gain in weight was enjoyed by 4 patients, 2 showed no essential weight change, and 1 (Case 7) had a marked drop in weight. All but 1 admitted to an improvement in appetite and sense of well-being. Glossitis disappeared within a week. Diarrhea, a persistent complaint in 4 patients, was much better controlled by folic acid than by liver. Within two weeks of starting folic acid, the patients exclaimed upon the decrease in number as well as bulk of stools. Those who had suffered diarrhea at night as well as in the daytime were improved until they could sleep without interruption. Diarrhea ceased completely in 1 severe case. The other patients began to enjoy periods of normal bowel habits alternating with periodic recurrences of diarrhea. Such recurrences were at long intervals and were preceded by ingestion of foods high in fat. The relief of abdominal distention was pronounced in the majority. All patients but 1 were enabled to perform normal work and earn a living. No neurologic disease or evidence of any harmful effect from the folic acid administration was seen. With the exception of Case 7, there were no relapses.

Regarding the chronicity of sprue, it has been our experience that about half the patients go into remission after initial treatment, and remain well for many years. On the other hand, there are a number of patients, like those in this report, whose histories of sprue extend back for several years and who have suffered various degrees of disability. These patients have been difficult to control. They have required close supervision of diet and specific therapy. Prior to the assay of folic acid in this group, purified liver extract given parenterally had been relied upon fairly satisfactorily as the chief mode of control. Injections of 30 to 60 units were given once to three times each week. Exacerbations occurred in the women during pregnancy despite maintenance liver therapy, and relapses were suffered by the men when an attempt to prolong the interval between injections of liver was made.

Folic acid, by comparison with liver extract, has proved to be of equal value, and perhaps superior in some cases, in the treatment of 6 of the 7 patients of this group. These patients followed essentially the same dietary regime while receiving folic acid as when taking liver extract. They were not

given supplemental vitamins, since, in our experience, these have proved worthless. Neither folic acid nor liver extract alone can be expected to be a cure-all in sprue. Folic acid can be given orally. This is a great convenience to the patient. Also, most of them dislike injection therapy.

By definition, the term sprue as used here designates the sprue syndrome as described by Hanes,⁴ and there seem to be no cogent reasons for attempting to differentiate the tropical and nontropical forms.

SUMMARY

Observations on the effects of folic acid given for at least a year to a group of sprue patients are presented. Folic acid has a beneficial effect in general, but does not produce complete remission in all types of cases. The majority of patients gained weight and had less diarrhea. One patient relapsed, with the development of weight loss, diarrhea and glossitis while receiving 60 mg daily. This case, however, was also refractory to purified preparations of liver extract and responded only to crude liver extract given intravenously.

Blood values were not quite so well maintained by folic acid as by liver extract, an experience encountered in a number of cases of pernicious anemia so treated. Three of the patients in whom folic acid was substituted for liver extract showed a drop in blood values over a period of a year. Despite this fact, they all experienced definite clinical benefits that had not been enjoyed while they had been on liver therapy.

The dosage requirements of folic acid varied from one patient to another. Whereas 15 mg daily sufficed for some, it was observed that increasing this dosage to 30 mg in other cases was followed by gain in weight and considerable relief of gastrointestinal symptoms.

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year later. Severe anemia was not a feature in any of the cases of this group. The blood picture in the majority was macrocytic, as judged by the stained films and the elevated mean corpuscular volume. In a patient who had at one time had a macrocytic anemia a hypochromic anemia developed. In our experience, which confirms that of others,⁵ the anemia associated with the sprue syndrome in many

to have multiple absorptive deficiencies. These included hypoproteinemia associated with edema, hypocalcemia accompanied by tetany, a flat glucose tolerance curve, subnormal levels of blood potassium and very low levels of plasma vitamin A, which did not rise after the administration of a large test dose of the vitamin. Not only was she refractory to folic acid but also purified preparations of paren-

TABLE 1 *Clinical Effects of Folic Acid in Chronic Sprue*

CASE No	PERIOD OF TREATMENT	NO OF STOOLS DAILY	CHARACTER OF STOOLS	TONGUE CHANGES	WEIGHT	APPETITE	ABDOMINAL DISTENTION	SENSE OF WELL BEING
					lb			
1	Before folic acid	2-3	Liquid frothy	0	152	Good	+	Fair
	After folic acid	1-2	Soft formed	0	152	Good	0	Improved
2	Before folic acid	1	Normal	0	101	Fair	0	Fair
	After folic acid	1	Normal	0	110	Good	0	Improved
3	Before folic acid	1-2	Soft, bulky	0	97	Poor	+	Fair
	After folic acid	1	Normal	0	104	Good	0	Improved
4	Before folic acid	4-5	Watery frothy	+	128	Poor	+	Poor
	After folic acid	1	Formed	0	141	Good	0	Improved
5	Before folic acid	3-4	Liquid bulky	+	128	Poor	+	Poor
	After folic acid	1-2	Soft-formed	0	129	Fair	+	Improved
6	Before folic acid	2-3	Bulky, watery	0	108	Fair	+	Fair
	After folic acid	1-2	Soft, foul	0	112	Improved	0	Improved
7	Before folic acid	7-9	Liquid, bulky	0	99	Fair	+	Poor
	After folic acid	7-9	Unchanged	+	67	Worse	+	Worse

cases is resistant to all forms of treatment. Strictly normal blood values have not been obtained despite the use of both purified and crude liver extract, iron and vitamins.

The effect of folic acid in maintaining blood values in patients who had received the conventional sprue therapy is shown in Table 2. Here it is

teral liver in large doses proved ineffective. Only after the frequent administration of massive doses of crude liver extract, "intraheptol," given intravenously were we able to induce a remission.

Clinical Effects

In Table 1 the clinical changes as well as the dosage of folic acid employed are listed. All pa-

TABLE 2 *Blood Values before and after Folic Acid*

CASE No	PERIOD OF TREATMENT	HEMOGLOBIN	RED CELL COUNT	HEMATOCRIT	MEAN CORPUSCULAR VOLUME	THERAPY
		gm/100 cc	$\times 10^6$	%	cu microns	
1	Before folic acid	13.5	4.40	44	100	15 units of liver extract intramuscularly each week
1	After folic acid	14.2	4.50	44	98	30 mg of folic acid daily
2	Before folic acid	15.0	5.00	47	92	None
2	After folic acid	13.6	4.55	44	96	15 mg of folic acid daily
3	Before folic acid	15.0	4.64	44	94	None
3	After folic acid	13.0	4.60	42	91	30 mg of folic acid daily
4	Before folic acid	13.1	3.82	44	112	None
4	After folic acid	13.5	4.45	42	94	30 mg of folic acid daily
5	Before folic acid	13.0	4.86	39	81	45 units of liver extract intramuscularly each week
5	After folic acid	11.5	4.00	36	90	30 mg of folic acid daily
6	Before folic acid	13.5	4.35	42	97	30 units of liver extract intramuscularly each week
6	After folic acid	12.2	4.00	36	90	30 mg of folic acid daily
7	Before folic acid	9.3	5.00	34	70	15 units of liver extract intramuscularly each day
7*	After folic acid	10.0	3.45	30	87	60 mg of folic acid daily

*This patient subsequently responded to crude liver extract administered intravenously.

noted that the hemoglobin, red-cell count and hematocrit were lower in Cases 5, 6 and 7 after a year of folic acid. In Case 7, despite a daily dosage of 60 mg, folic acid proved a complete failure. The patient steadily lost weight, her appetite declined, steatorrhea and diarrhea continued, she developed glossitis, and her state of relapse was so severe that she was hospitalized. She was found

patients received the same preparation of folic acid in tablets orally. Contrary to reports by certain other investigators that doses as low as 5 mg daily suffice for most cases, that amount was totally inadequate in our cases. On such small doses, the patients exhibited only a fraction of the degree of improvement seen after an increase to 30 mg daily.

acquires reactivity to what is a variant of LH or is a new pituitary gonadotropin, luteotropin. Hisaw's fourth stage of development, that of the corpus luteum, begins

Meanwhile the ovum has matured and, in its first mitotic division, has split its chromosomes longitudinally and extruded half their substance in a polar body. The follicle ruptures, floating out the mature ovum on the liquor folliculi (described below). With rupture the luteinization that started the third stage of follicular maturation continues. More progesterone, as well as estrogen, is secreted. As estrogen continues to suppress FSH production by the anterior pituitary body, LH and its successor, the luteotropic hormone, acquire ascendancy and establish the corpus luteum. For about ten days this produces gradually increasing amounts of estrogen and of progesterone. After the first week it starts morphologic regression, for it loses susceptibility to further stimulation by pituitary gonadotropins. Only chorionic hormone, secreted by the trophoblast of the differentiated conceptus, can revive this declining gland.

Meanwhile, what has happened to the several other graafian follicles that by estrogen had been sensitized to FSH and had begun to grow? They reached that degree of maturity at which they were ready to start luteinization — Hisaw's third stage of development. They failed to qualify at this point because of a delicate species quality. In the human subject there seems to be just enough LH in co-operation with FSH to evoke effective amounts of progesterone and increased estrogen in only the most receptive follicle. This most sensitive follicle takes all there is, and its resultant endocrine activity diminishes the hypophyseal product below the reactive threshold of the other follicles or progesterone desensitizes them to the FSH and LH present. It is known that these other thecated follicles regress, leaving only those with well developed antra but without well luteinized thecae internae.

Thus it is in human beings that, typically, only one follicle ruptures, other competing follicles regress. Time is required after the corpus luteum involutes for more follicles, by their own estrogen, to become successively responsive to FSH and to LH that gradually increase when the regressing corpus luteum diminishes its production of estrogen and progesterone, which respectively had inhibited the very hypophyseal activity that evoked each of them.

OVULATION

The accumulation of liquor folliculi within the distended granulosa and theca of the maturing follicle may increase the internal pressure. Were this so, something must give or the granulosa and the ovum would be crushed. Perhaps the pressure is transmitted through the concentric muscled laminations of the thecae interna and externa to the less organized stromal connective tissue, surround-

ing the follicle. This would then recede before the stress of the follicle and its supporting thecae. At all events, unless only superficial follicles mature, the whole growing graafian unit moves toward the surface. It bulges as the cortical germinal layer and the underlying thecal layers as well become thinner. Finally, the continuity of these surface layers is broken, and the fluid escapes. Floating out with it are the disrupted portions of the granulosa and cumulus. In the latter is the ovum within its zona radiata of more cohesive granulosa cells. Recently, Kraus⁷ experimented with rabbit follicles in an attempt to determine the factors of rupture. From these experiments it was deduced that not internal pressure, local enzymatic action, muscular force in the theca or "pull" of the cilia of the fimbria was involved. It was therefore postulated with proper serenity that there occurred a 'morphologic change in the stigma' of unknown nature and caused by unknown agents.

Time of Ovulation

As is common, with only rare exceptions, to all species of animals studied, a short individual life is the lot of human germ cells. To serve their function those of the two sexes must unite within a number of hours after being freed, the ovum from the ovary and the sperm from the male genital tract. The chance of conception in human beings is exceedingly slight, indeed perhaps impossible, if the nearest *preceding* coitus occurs more than forty-eight hours before ovulation, and the first *succeeding*, more than twelve hours after escape of the egg. Once meiosis, the process of diminution of chromosomes, has begun, as it does usually in the follicle with the first polar division, it progresses steadily. When terminated in the tube, probably at most twenty-four hours later, more chromosomes, to complete the species number, must soon be added or life processes cease. Furthermore, it seems likely, from studies such as that of Blandau and Young⁸ in the guinea pig and those of several others in different species, that if ova approaching deicide do become activated, or if an aged sperm succeeds in fertilizing an ovum, the resultant conceptus is very likely to be defective. It is of great practical importance, therefore, to know just when in the menstrual cycle ovulation takes place.

The number of independent biologic factors involved in the whole process of ovulation from beginning luteinization of the theca interna to the final rupture of the mature follicle makes evident the probability that no sign of the exact moment of ovular release will ever be recognizable. Ovulation is the result of the interplay among hormonal agents such as carefully adjusted proportions of FSH and LH, physical agents such as accumulation of fluid in the follicle and migration of this enlarging cyst to the cortex, and possibly enzymatic agents or even the more obscure internal "cell organizers"

MEDICAL PROGRESS

PHYSIOLOGY OF HUMAN CONCEPTION*

JOHN ROCK, M D †

BOSTON

ALTHOUGH simple parthenogenesis is not at all uncommon in invertebrates — for instance, in ants and bees — it does not, as far as is known, occur in human beings, who must produce eggs and sperm and then effect their conjugation. The following discussion concerns itself only with the somatic aspects of this complicated process since the beguiling psychologic motivation and mechanisms lie in a mixture of too much fancy with too little fact.

Among various vertebrate species the sequential involvement of the primordial oocyte, within its epithelial capsule, to the mature ovum, in the rupturing follicle, is impressively similar, although the duration of the successive phases may be very different. We are thus led to believe that, in human beings, factors identical with those recognized in laboratory animals are involved in the growth process. There is no specificity of pure hormones, for those from one animal are effective in others. The degree of their potency and the susceptibility of the target organs, however, vary widely among species. Of the gonadotropic hormones found effective in animals some are known to be produced likewise in human beings, and others are reasonably assumed to be. Doubtless their effects in human beings are the same, in kind, if not in degree.

In the human ovary at puberty there are said to be, distributed through the stroma, more than 10,000 ova in various stages of development.¹ Some are small oocytes surrounded by a single layer of epithelial cells. These nurse cells, the precursors of the granulosa, and the central oocyte are believed to be derived from the mesothelium that covers the original formative gonad. This mesothelial derivative becomes the germinal epithelium. Whether in human beings all primitive ova are present at birth or new ones, from time to time, descend from the germinal layer into the cortex is not known. Hartman² has shown that oogenesis continues in the rabbit, and Allen³ that this is so in the mouse, and Mossman⁴ states that it occurs in the pocket-gopher. Although Hertig⁵ has not incidentally seen mitotic activity in the germinal layer of any mature ovary it seems at least possible that production occurs, albeit infrequently, in adult life.

*From the Fertility and Endocrine Clinics, Free Hospital for Women, Brookline, Massachusetts, and the Department of Gynecology, Harvard Medical School.

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†Clinical professor of gynecology, Harvard Medical School, visiting surgeon and director of Fertility and Endocrine Clinics, Free Hospital for Women, Brookline, Massachusetts.

MATURATION OF THE FOLLICLE

Hisaw⁶ has recently reviewed pertinent follicular biology in animals and from his discussion one may plausibly theorize on this process in patients and, complacently ignoring the absence of many proofs, describe it as follows. Governed by a "self-contained system of organizers," the primordial oocyte while attaining full size, effects an investment of several layers of granulosa cells from the primitive epithelium surrounding it. This simple group of ovum and nurse cells causes the adjacent connective tissue to develop the theca interna. This, then, consists of a specially vascularized tissue of enlarged cells, which sooner or later, and again, automatically, by reason of their own intrinsic enzyme system, secrete estrogen.

The estrogen from the theca interna now empowers the granulosa layer to produce a fluid that it holds within a small, newly formed antrum. The appearance of this small vesicle terminates Hisaw's first stage, and ushers in the second stage of follicular development.

Estrogen thus appears as the indispensable self-organizer of the graafian unit. After responding to estrogen the follicle "gains competence" to react to the follicle-stimulating hormone of the hypophysis (FSH). This requirement of preliminary conditioning by estrogen explains why some follicles mature and others do not, for it is FSH that stimulates gross enlargement of the vesicle, but only after estrogen has first primed the granulosa and possibly its source, the theca itself. Estrogen also has other targets. It induces the hypophysis gradually to quit production of FSH and to secrete luteinizing hormone (LH). It is now apparent that both LH and the previously secreted FSH act on the theca to start the luteinizing process.

With the well developed follicle, about 1 cm in diameter, Hisaw's third stage begins. As this progresses, more estrogen, together with gradually increasing amounts of progesterone is secreted by the theca, and the follicle extends its growth toward maturity. It enlarges to a diameter of even 2 cm by the accumulation of fluid, the increasing estrogen reacts on the hypophysis to diminish its production of FSH and to bring forth more LH. As these combined gonadotropins act on the follicle most sensitized by estrogen and previous FSH, this one secretes more progesterone. Furthermore, it

acquires reactivity to what is a variant of LH or is a new pituitary gonadotropin, luteotropin. Hisaw's fourth stage of development, that of the corpus luteum, begins.

Meanwhile the ovum has matured and, in its first mitotic division, has split its chromosomes longitudinally and extruded half their substance in a polar body. The follicle ruptures, floating out the mature ovum on the liquor folliculi (described below). With rupture the luteinization that started the third stage of follicular maturation continues. More progesterone, as well as estrogen, is secreted. As estrogen continues to suppress FSH production by the anterior pituitary body, LH and its successor, the luteotropic hormone, acquire ascendancy and establish the corpus luteum. For about ten days this produces gradually increasing amounts of estrogen and of progesterone. After the first week it starts morphologic regression, for it loses susceptibility to further stimulation by pituitary gonadotropins. Only chorionic hormone, secreted by the trophoblast of the differentiated conceptus, can revive this declining gland.

Meanwhile, what has happened to the several other graafian follicles that by estrogen had been sensitized to FSH and had begun to grow? They reached that degree of maturity at which they were ready to start luteinization — Hisaw's third stage of development. They failed to qualify at this point because of a delicate species quality. In the human subject there seems to be just enough LH in co-operation with FSH to evoke effective amounts of progesterone and increased estrogen in only the most receptive follicle. This most sensitive follicle takes all there is, and its resultant endocrine activity diminishes the hypophyseal product below the reactive threshold of the other follicles or progesterone desensitizes them to the FSH and LH present. It is known that these other thecated follicles regress, leaving only those with well developed antra but without well luteinized thecae internae.

Thus it is in human beings that, typically, only one follicle ruptures, other competing follicles regress. Time is required after the corpus luteum involutes for more follicles, by their own estrogen, to become successively responsive to FSH and to LH that gradually increase when the regressing corpus luteum diminishes its production of estrogen and progesterone, which respectively had inhibited the very hypophyseal activity that evoked each of them.

OVULATION

The accumulation of liquor folliculi within the distended granulosa and theca of the maturing follicle may increase the internal pressure. Were this so, something must give or the granulosa and the ovum would be crushed. Perhaps the pressure is transmitted through the concentric muscled laminations of the thecae interna and externa to the less organized stromal connective tissue, surround-

ing the follicle. This would then recede before the stress of the follicle and its supporting thecae. At all events, unless only superficial follicles mature, the whole growing graafian unit moves toward the surface. It bulges as the cortical germinal layer and the underlying thecal layers as well become thinner. Finally, the continuity of these surface layers is broken, and the fluid escapes. Floating out with it are the disrupted portions of the granulosa and cumulus. In the latter is the ovum within its zona radiata of more cohesive granulosa cells. Recently, Kraus⁷ experimented with rabbit follicles in an attempt to determine the factors of rupture. From these experiments it was deduced that not internal pressure, local enzymatic action, muscular force in the theca or "pull" of the cilia of the fimbria was involved. It was therefore postulated with proper serenity that there occurred a "morphologic change in the stigma" of unknown nature and caused by unknown agents.

Time of Ovulation

As is common, with only rare exceptions, to all species of animals studied, a short individual life is the lot of human germ cells. To serve their function those of the two sexes must unite within a number of hours after being freed, the ovum from the ovary and the sperm from the male genital tract. The chance of conception in human beings is exceedingly slight, indeed perhaps impossible, if the nearest preceding coitus occurs more than forty-eight hours before ovulation, and the first succeeding, more than twelve hours after escape of the egg. Once meiosis, the process of diminution of chromosomes, has begun, as it does usually in the follicle with the first polar division, it progresses steadily. When terminated in the tube, probably at most twenty-four hours later, more chromosomes, to complete the species number, must soon be added or life processes cease. Furthermore, it seems likely, from studies such as that of Blandau and Young⁸ in the guinea pig and those of several others in different species, that if ova approaching deicide do become activated, or if an aged sperm succeeds in fertilizing an ovum, the resultant conceptus is very likely to be defective. It is of great practical importance, therefore, to know just when in the menstrual cycle ovulation takes place.

The number of independent biologic factors involved in the whole process of ovulation from beginning luteinization of the theca interna to the final rupture of the mature follicle makes evident the probability that no sign of the exact moment of ovular release will ever be recognizable. Ovulation is the result of the interplay among hormonal agents such as carefully adjusted proportions of FSH and LH, physical agents such as accumulation of fluid in the follicle and migration of this enlarging cyst to the cortex, and possibly enzymatic agents or even the more obscure internal "cell organizers."

that cause final dissolution of continuity in the wall of the follicle and in its thinned-out cortical cap. It seems unlikely that all of these are trigger mechanisms, which function with exact time relations to each other. It is of great interest in this connection, on the other hand, that Sawyer, Markee and Hollinshead⁹ have shown that the hypophysis in the rabbit responds to the coital stimulus within at most three minutes. It has long been known that, in rabbits, follicles rupture from ten to fourteen hours after coitus. But even in rabbits the exact time of ovulation is not easily detectable without inspection of the ovaries. An indicative change in electropotential was reported by Burr et al.¹⁰ and Reboul, Friedgood and Davis,¹¹ but this is not a useful method even in rabbits, and Snodgrass¹² has shown it to be quite undependable in human beings.

In the monkey and the cow the approximate time of ovulation, within hours, may be determined by repeated palpation of the ovary through the rectum—a method not likely to be practical with patients. Except in rare cases “mittelschmerz” is quite unreliable. The specific cause of the pain is unknown, so that even in the occasional case in which it is so peculiar as to be unmistakable it can do no more than indicate the process of ovulation and not the actual event.

It is now generally admitted that ovulation occurs about two weeks before the manifest onset of normal menstruation. This must be so, for flow is precipitated by withdrawal of corpus luteum hormones, and the corpus luteum may be said to acquire definitive form and function within perhaps a day of ovulation, and to remain active for about two weeks. The duration of luteal dominance is deduced from observation of the effects of its specific product, progesterone, on the endometrium,¹³ by detection in the urine of pregnanediol,¹⁴ an excretion product of progesterone,¹⁵ by proportional changes in urinary estrogens¹⁶ and by cytologic and histochemical study of corpora lutea themselves.¹⁷ Comparison of previllous human conceptuses with those of the macaque, in which the actual ovulation ages are known, because the actual day of ovulation had been determined by Hartman's method of bimanual rectal palpation, gives final confirmation to the deduction that human ovulation occurs *about* fourteen days before the first day of normal menstruation.¹⁸

Consideration of the inexactness of all these data is salutary. In the cytologic studies of the endometrium, in the biochemical assays of excretion products and in the cytologic and histochemical studies of corpora lutea, the results pointing to about fourteen days of function either were averages of findings or were postulated from a theoretical date of ovulation and then found to agree with this date within a statistically significant limit of error. The constancy of the agreement was hence taken to

substantiate the theoretical date. In the case of the actual conceptuses whose ovulation ages could be determined fairly accurately, the time between the day of ovulation and the onset of menstruation had to be estimated, for, of course, in the particular pregnant cycle, there was no subsequent menstruation. The dates when catamenia would have occurred were arrived at by reference to each mother's previous menstrual cycles, which are generally constant within an inclusive range of 5 days.

In 1937 Rubenstein¹⁹ revived interest in the fact that during most menstrual cycles the curve of daily basal temperatures is diphasic, lower in the first part of the cycle than in the second. He correlated the shift in temperature levels with changes in the vaginal smear that had been shown by Shorr and Papanicolaou²⁰ to be attributable to ovarian function. In 1944 Klasten showed,²¹ by experiments with amenorrheic women, that the increase in temperature was a function of progesterone. Thus, it is now generally believed that when the temperature rises to stay it may be assumed that the corpus luteum is functioning and, so, that ovulation has occurred.

To minimize disturbing factors the temperatures recorded are best taken each day promptly on awakening and before any activity beyond placement of the thermometer. For those who are careful, mouth temperatures give informative curves, but for most women rectal or vaginal readings are more dependable. There is no uniformity in the curves of women in general, except that during the ovulatory cycles they are diphasic. Indeed, among succeeding ovulatory cycles in the individual woman, the temperature levels and the gradients may both be noticeably dissimilar. Examination of the completed curves, however, will usually reveal either the sudden or the gradual termination of the lower first phase. The day or days of the last lowest temperature from which, either abruptly or by stages, it rises to stay are generally taken to be the day or days of the ovulation phase. Only very rarely does one see a chart in which this apparent sign of ovulation is beyond the limits of 14 ± 4 days before the onset of flow. In most women this assumed ovulation phase is found to lie usually within the range of 14 ± 2 days before menstruation, but every woman is likely to stray out of range every now and then.

TUBAL FUNCTION

Whence goes the 1, 2 or even 6 cc. of liquor with its indispensable egg when it escapes from the follicle? It must flow into the variable amount of peritoneal fluid that bathes all viscera. Doubtless it is not infrequently dispersed about the pelvis, washing the ovum to distant places beyond the reach of spermatozoa. To prevent this in some mammals there is an ovisac, surrounding the ovary, a delicate serosal receptacle attached to and open-

ing into the tube Human beings have not thriftily acquired this little catchbasin that would prevent loss of eggs, they have a more complicated and defective mechanism

The fimbriae of the tubes vary widely among women Some consist of short and closely approximated growths of ciliated epithelium on a narrow, flat collar of muscled connective tissue surrounding the ostium This collar may have a radius of less than 1 cm Sometimes the flared end of the tube is found to have a long fringe that may extend outward to a radius of 2 cm (especially on the abovarian margin) This fimbriated structure is important, and modification of the ideal wider collar may be very significant to fertility Westman²² has credibly postulated that as ovulation approaches, muscle fibers in the tubo-ovarian ligament contract to approximate the fimbria to the ovary and that, furthermore, other muscle fibers in the thin connective-tissue collar spread out this structure so as to engross the ovary in a curved, fan-shaped envelope, which constitutes a homologue of the ovisac of some so-called more primitive animals Careful exposure of adnexa at laparotomy during the ovulatory phase often discloses both ovaries thus covered

Improving this system of receptivity is the ciliated mucosa that forms the surfaces of this extension of the ostial border adjacent to the ovary In functional position this epithelium faces the ovary, and the beating cilia establish a current from the ovary and the pelvic cavity toward the uterus Physiologically, the liquor folliculi is pulled toward the tube Carried in the liquor, the ovum in its tattered vestment of granulosa doubtless thus floats into the ampulla, when the system works Otherwise, and perhaps more often than has been thought, the liquor is dissipated and the ovum lost in the pelvis

The quality of tubal fluid with regard to the egg may be very important, but at the moment all one knows is that it offers a warm, moist medium in which the ovum may be fertilized and conveyed to the uterus Mouse ova, removed from the tube and placed in the anterior chamber of the eye,²³⁻²⁴ have achieved implantation there Rat ova, similarly obtained and properly placed, have implanted under the capsule of the kidney²⁵ Once fertilized, neither apparently suffered by deprivation of tubal fluid²⁶

Judging by 4 activated human eggs cultured *in vitro* and 1 human incipient morula found in the uterus, there is little if any increase in protoplasmic bulk up to the 4-cell stage Between this and the 8-cell stage the vitelline mass apparently does grow, but probably in human beings this growth occurs in the uterus (The mouse eggs observed by Lewis and Wright,²⁶ as well as the rat eggs studied by Alden,²⁷ may have increased in size in the tube)

It appears that tubal fluid may be not only a protective covering and vehicle for the egg but also

a substrate delicately adjusted in pH and osmotic pressure for the fertilization process and, too, a nutrient medium for ova The possibility that the ovum makes respiratory demands on this tubal product must be considered, but of this nothing is really known

Sojourn in the tube is fairly short A 4-cell human morula, possibly abnormal, but yet not more than four days old was found by Hertig⁵ in the uterine cavity Two other human conceptuses between seven and eight days of age, both doubtless normal, were found to be so well embedded in the endometrium as to indicate that nidation had been started not later than the sixth postovulatory day There seems good reason to believe, then, that the antrum-containing blastocyst takes shape about the fifth day and that at this time the new organism must be where the rapidly differentiating trophoblast will be offered appropriate nidation How does it get there?

The tube is roughly seven hundred times longer than the diameter of the inert egg (100 μ m versus 0.150 mm) The comparatively long haul to make delivery in the uterus is accomplished by downward propulsion of the fluid carrier with its cargo by the ciliated endosalpinx, doubtless aided by the more effective peristalsis of the myosalpinx During the few days of its journey the single cell, by mitotic division of the vitellus, changes into at least or at most a 4-cell morula Some time after this cleavage the jelly-like pellucida disappears Fawcett²⁴ and Runner²⁸ have called attention to the fact that even for this process neither the tubal fluid nor the uterine fluid is necessary in the mouse and rat, for this structure is equally well disposed of in such foreign places as the eye, the kidney or the peritoneal cavity

The tubes also serve the spermatozoa as conduits at least How the motile organisms progress through them is considered below Here it is pertinent to note that there is reason to suspect that, in the rabbit, tubal fluid supplies an enzyme system that conditions the sperm for facile entry into the vitellus through the vitelline membrane²⁵ Such a possible biochemical process must be nicely integrated with the probable antigen system effecting conjugation so carefully studied by Loeb,²⁹ Tyler³⁰ and others, mentioned below under "Fertilization"

UTERINE FUNCTION

As segmentation progresses, the conceptus increases in bulk it takes something from the thin layer of fluid separating the anterior and posterior surfaces of the endometrium This must include metabolites as well as water, but of their nature little is known beyond the fact that starting about four days after ovulation, or about the time the ovum reaches the fundus, the uterine glands discharge a secretion containing glycogen During the fifth day progressive cell division of the

blastocyst results in differentiation into two kinds of tissue. One forms the inner cell mass, which projects into the newly formed antrum. This will develop into the embryo proper. The other specialized group of cells is the outer trophoblast, which constitutes the wall of the antrum. The latter tissue apparently secretes some substance that causes vasodilatation and even extravasation of blood in the neighboring maternal tissue, which, normally, is the endometrium.²⁴ The outer, or syncytial, trophoblast at the embryonic pole also engorges the surface epithelium as it "forages" its way toward the vessels in the stromal bed underneath.²¹ In the human being it goes farther. In the youngest implanted specimen, barely seven days old, one sees the syncytium phagocytizing stromal cells as well, while the whole organism is gradually enclosed within the endometrium. Judging from the effect of the trophoblast on several different tissues, — the iris,²³ the kidney capsule,²⁵ the peritoneum, the endosalpinx and the endometrium, — access to maternal blood is the ultimate objective. While struggling on to this complete food, the trophoblast must be nourished by contributions from intercellular fluid and from the ingested stroma cells. The biochemicals, necessarily found here, have not been identified except for phosphatases, glycogen and some lipids.²²

There seems little doubt that whatever the food material is, its presence is caused by progesterone and estrogen from the corpus luteum. It was stated above that the corpus luteum of the nonpregnant cycle ceases further growth after about the seventh day following ovulation, for then its ability to respond to pituitary gonadotropins has reached its peak. If conception has occurred, however, the sequence changes. Until the definitive placenta is formed — that is, until there is plenty of maternal blood available to fetal villi capable of utilizing it, — the trophoblast must be sustained partly by maternal blood that enters the lacunae and also by endometrial fluid and cells. On the seventh day the conceptus is barely embedded. Villi are not recognizably started until it is about fourteen days old. During the week intervening, and indeed for several weeks later, while the fetal portion of the placenta is establishing itself, the corpus luteum is maintained, providing increasing amounts of progesterone and estrogen. This perpetuation of the corpus luteum is brought about by a gonadotropin secreted by the trophoblast, the so-called chorionic hormone. The continuance of luteal activity by this fetal hormone substantiates the decidua, which would break down in menstrual disintegration were its supporting hormones, progesterone and estrogen, withdrawn. This must be prevented not only because this tissue with its juices sustains the growing trophoblast but also, perhaps primarily, because it serves as the protecting matrix within which the

ever-increasing vascular bed of the maternal part of the placenta is forming.

The versatile trophoblast eventually assumes an added function. At some time between the first and the eighth week of gestation (the twenty-fifth day in monkeys)²² it takes over the work of the corpus luteum and secretes its own large amounts of progesterone and estrogen throughout the allotted remainder of pregnancy, thus continuing the support of the decidua and the maternal placenta.

Aside from the fact that spermatozoa utilize carbohydrates and produce carbon dioxide, their metabolic processes are almost unknown. Compared to their size they must use a great deal of energy. Do they get their source material from the uterine and tubal fluids? After ovulation the endometrial glands secrete a glycogen-bearing mucus. This comes too late for the fertilizing agents. The food stuffs that are mobilized into and out of the endometrium and the various enzymes and their adjuncts that accomplish this are being studied in several research centers. It will be known in time what are the requirements in their medium for the spermatozoa, and then, doubtless, methods of detecting whether or not essentials are present. In the meantime one can only postulate the necessary presence there of some easily utilizable glucose, and, in the spermatozoa, the enzymes, adapted for its use.

CERVICAL FUNCTION

The cervix, which constitutes the portio or passage way to the uterus from the vagina, ideally enters this muscled sheath for the functioning penis in the rear of its superior wall, about 8 cm from the posterior border of the symphysis. So variable are the length of the vagina and the position of the uterus in the pelvis that the portio may lie anywhere in the superior or posterior wall. It never enters from below. Furthermore it may point forward or downward instead of in its normal direction, backward. As can be observed through a glass obturator of a caliber similar to that of the phallus, about 4.5 cm, stretching of the vaginal walls as occurs during coitus brings the attached cervix into the axis of the vagina, except when the portio lies within about 5 cm of the symphysis. In such cases the penis by-passes it, and ejaculation doubtless hits the posterior wall. Consideration of the following remarks about insemination will suggest that, except when maladaptation is extreme, the position of the cervix is probably of but slight significance. In about any position it can serve its only apparent function, which is to produce a quantity of favorable fluid that, mixing with the ejaculate, still maintains continuity through the canal with the fluid of the fundus.

While estrogen from the growing follicle is causing proliferation of the endometrium, it is also cultivating the endocervical mucosa. Just after

menstruation the mucous excretion from the cervix is scant, very viscous, sometimes even gelatinous and replete with epithelial cells and granular debris. At some time during the week preceding ovulation, when estrogen secretion is mounting, the cervical product increases in amount and decreases in viscosity and cell content. Throughout the phase of ovulation it is normally plentiful, grossly clear as water and of comparatively low viscosity. Careful exposure of the cervix at this time reveals it bathed in this alkaline polysaccharide that before degeneration is easily penetrable to spermatozoa. So copious is the normal production of this fluid that it spreads outward through the vagina and sometimes even rises over the perineal body to bathe the introitus.

SEMEN

Now, what of the man? Spermatozoa are produced continuously through adult life by the germinal epithelium lining the seminiferous tubules. Fully grown, but immature in some one or several metabolic capabilities required for fertilization, they congregate in the tubules until, with their successors, they are moved out into the epididymis. In the almost interminable coils of this organ the fairly solid mass of closely approximated inactive germ cells is propelled onward, again possibly by the pressure behind of newer organisms, and possibly also by peristalsis of the tubular walls. Here in the epididymis some obscure maturing or complementing process takes place. In the vasa the column moves still onward, the cells here also improving, but still more or less inactive, until either those in the vasa gradually spill over into the posterior urethra to be washed out in the urine or a large part of the whole column is ejected through the ejaculatory duct in the first phase of ejaculation.

As Hotchkiss²⁴ properly complains, "the exact physiology of the mechanism of ejaculation has not been ascertained." Apparently, within a split second of their arrival, thus, in the posterior urethra, they are joined by a little secretion from the promptly contracting prostate and perhaps vesicles and almost immediately this mixture, made up largely of spermatozoa, is vigorously propelled, ideally, to the cervical os. The total ejaculate varies in amount from about 3 to about 9 cc. and normally contains about 500,000,000 spermatozoa. Recurrently, contractions of the penile muscle discharge the mixed portions, but with each successive ejaculation the concentration of spermatozoa diminishes while the proportion, not the amount, of prostatic and vesicular increment increases.

Thereafter the prostate and vesicles together with the vasa start to replenish their secretions, and the vasa their supply of sperm. The respective characteristic contents of these accessory organs, both in volume and constituents, however, are not re-

established usually within two days, and, in some men past the primal late teens and twenties, possibly not within four days. A second total ejaculation within hours of the first contains comparatively few spermatozoa and a diminished amount of fluid.

Physiology of the male generative tract is still lamentably obscure. (Every gynecologist dealing with infertility should read carefully Hotchkiss's²⁴ chapters on this subject, for then he can keep both himself and his ethical and conscientious urologic consultant from subjecting distraught and hence credulous couples to plausible but futile, troublesome and expensive procedures and medication.)

The seminal vesicles and prostate function under the influence of the male sex hormone. The former produce a mucoid substance rich in sugars among other chemicals, and sperm have been shown by MacCleod²⁵ to acquire their energy by utilization of the sugar thus provided. Mention must be made of the enzyme, hyaluronidase, that may be a factor in denudation of the granulosa vestment of the ovum. It is possible that this, or a precursor of it, comes from the secretions of either prostate or vesicles, for it is somehow acquired by the spermatozoa. This subject is further discussed below under "Fertilization."

Furthermore, Chang²⁶ has recently noted that the ability of rabbit sperm to activate ova may be dependent on some substance contained in the seminal substrate. Perhaps this also comes from some one or other of the accessory male organs. Munro²⁷ showed that in fowl less than 1 per cent of ova were fertilized by sperm from the testicle, whereas 63 per cent were fertilized by sperm from the efferent ducts. Does the substance postulated by Chang come from the vasa? (As stated above, Finkle²⁸ proposes that tubal fluid may also improve the effectiveness of rabbit sperm.)

COITUS

Human copulation does not lend itself easily to scientific investigation, and what is known of the process in other mammals is not very helpful. The genital anatomy of human beings is quite different in important details from that of even the other primates. I know of no authoritative description of what actually happens in the human vagina during coitus and at ejaculation nor of the behavior and progress of spermatozoa from the time they leave the penis until one penetrates the ovum. I may therefore be permitted to surmise, trying always to restrain my imagination by a few actual observations.

It may be conjectured that during coitus the recurring thrusts and retractions of the penis cause the vaginal walls alternately to approximate and separate from the portio, thus serving, with the intermittent contact of the glans to cervix, to spread much of the cervical mucus on to the vaginal wall. If this is so, the external os is thus partially cleared of

excess and sometimes opaque degraded secretion such as is commonly seen about the portio. The forceful impact of the first ejaculated mass of spermatozoa and a little seminal fluid against the layer of mucus that covers the deeper vagina and the portio joins these two viscous liquids. Movements of the penis mix them, as continued discharge of alkaline semen containing a few more spermatozoa places such a quantity of material in the vagina as will spread over its walls, when these again become contiguous on withdrawal of the penis. Spermatozoa are thus protected from the usual acidity of the vaginal desquamate.

I do not know what constitutes female orgasm. Perhaps contractions of the myometrium are a component, and perhaps subsequent relaxation contributes a pull on material in the cervix and at the external os. Whether or not this is so is not clearly significant, for there is no doubt that, other factors being adequate, conception is easy without female orgasm.

The stratified epithelium of the vagina is highly absorbent. After coitus some of the ejaculate may be taken up, some is slowly extruded through the introitus as the vaginal walls contract. Active spermatozoa produce carbon dioxide. Gradually, the acidity of the vaginal content is re-established, and after four hours all spermatozoa therein cease motility and probably die.

INSEMINATION

When, as is normally the case, some 500,000,000 spermatozoa are originally present in the fluid that, on withdrawal of the penis, is spread over the vaginal walls, several hundred thousand will by chance find their way into the cervical canal before they succumb.

The mixture of semen with mucus from the cervix is continuous with the column of clear secretion in the cervical canal, as this in turn connects with the thin layer of mucoprotein from the endometrium. Until there is evidence, now completely lacking, that some chemotropic, rheotropic or electrotropic force directs their movements, it must be supposed that spermatozoa swim aimlessly in the widespread vaginal pool, the deepest part of which, containing most of the spermatozoa, is that into which the portio projects when this is normally placed at the end of the vagina.

Observation of the post-coital content of the cervix shows clearly that its secretion at ovulation time offers a very favorable substrate for spermatozoa. In the ovulatory phase, even forty-eight hours after ejaculation, normally progressive organisms are not infrequently seen in great profusion in cervical mucus. About sixteen hours after coitus each high-power field of fluid from within the cervical canal may contain from 10 to several hundred organisms.

At other times in the menstrual cycle sperm from a normal ejaculate may or may not penetrate the

cervical product. Occasionally one sees a woman in whom the endocervical mucus almost throughout the cycle secretes a fluid low in viscosity and cellular debris. Penetration by sperm is not as uniform or as extensive as it is normally at ovulation time, nor do those organisms that do enter the cervix apparently find therein a medium that satisfies their needs. They may remain active for twelve or more hours, but usually few are progressively migratory even six hours after coitus.

We may assume that some spermatozoa, highly activated by what they utilize from their ejaculated substrate, still as if aimlessly, find their way from the cervical mucus into the fundus and there deploy. Here is a broad, thin layer of fluid lying between anterior and posterior walls, which connect along the edges in an arc so acute that they would touch one another were it not for the shallow lake of secretion interposed between them. Where the lateral shores of this triangular lake meet the basal fundal border are the two tiny inlets of the tubes. As one watches active spermatozoa in a hanging drop one sees large numbers of the more normal ones gather along the edges, heads out and thrashing tails inward. In this so-called phalanx formation, individual sperm move sideways along the border, sometimes in one direction, sometimes in the other, but in general maintaining their outward orientation. Perhaps by a similar tendency in the uterus sperm may gather along the shore and some of these, perchance, come across the tubal ostia and swim into them.

Progress of sperm in a straight line in cervical mucus has been measured as about 1 mm per minute. A direct line from the external os to the opening of the tube is perhaps about 120 mm — a two-hour trip. Spermatozoa were found in the tube by M. Edward Davis³⁸ about three hours after coitus. If movement is truly random perhaps they move faster in the uterine medium.

In comparison to the size of the spermatozoon, the mass of the cervical and fundal body of fluid together with that in the vagina is so vast as to make it unlikely that a very high proportion of spermatozoa in any single ejaculate ever reaches the tubes. One might guess from the numbers seen in the cervical mucus after coitus that of the several hundred million placed in the vagina, only several hundred thousand reach the cervix. Of these probably some tens of thousands migrate into the fundus, and only a few thousand, at most, eventually enter the tubes.

Here they move upward by swimming against what to their vigor must be a very weak current if it is established only by the cilia of the endosalpinx. The generally downward progress of the tubal fluid — after ovulation, at least — is doubtless accomplished by peristalsis. The waves of this increase in magnitude during the ovulation phase. Just before and perhaps immediately after ovulation, when the necessary spermatozoon, along with

those that accompany it, must find its way to the outer ends of the tube, weaker and more frequent contractions of the myosalpinx might easily form eddies among the irregular rugae of the endosalpinx. In these inconstant but connecting pools the vigorously swimming spermatozoa might, with many slips backward, conceivably be helped onward. Parker⁴⁹ has studied the migration of sperm in several species of terrestrial vertebrates (turtle, pigeon and rabbit), in the rabbit, he attributes to the downward ciliary current along the edges of the endosalpinx a reverse central flow that facilitates upward progress. This may be the case in human beings, but, as demonstrated in the film of Somers Sturgis entitled "Observations on Some Factors Which Influence the Direction of Sperm Motility" (1946), the spermatozoa are so enormous and so strong in comparison to the force of the ciliary current, as, apparently, to disregard it. I should think that, if there is any tropism in action, peristalsis is the effective factor.

Of the few thousand spermatozoa from a single ejaculate that might enter the tubes, how many by these theoretical mechanisms reach the ampulla wherein to meet the ovum? Probably not more than a few hundred, or approximately one-hundredth of 1 per cent of the number in the ejaculate. Hence the handicap of oligospermia.

FERTILIZATION

As the inert ovum, still in its ragged zona radiata of granulosa cells, is gently rolled and pushed here and there along the opposing walls of the somewhat dilated outer end of the tube, more than likely, but not inevitably, it encounters a few of the few hundred spermatozoa thrashing about in the ciliary current.

While the second mitotic division is taking place — that is, while the second polar body is being extruded from the vitellus, after halving of the number of chromosomes — the zona radiata of granulosa cells is dispersed. Denudation of the zona pellucida is accomplished. This may be an important process for fertilization. The multicellular coating of the ovum is desirably removed or else the sperm must have great difficulty reaching the zona pellucida through which one enters the vitellus. The granulosa cells of the zona radiata are held together by a glucoside common to many other cell aggregates or tissues of the body, called hyaluronic acid. This adhesive substance is broken down by the enzyme, hyaluronidase, alluringly found in semen. This very useful agent, possibly also produced by the germinal epithelium,^{44 45} is taken by spermatozoa and freely relinquished whether or not they manifest life.⁴⁰ I have watched many human ovarian ova become denuded during culture in human blood serum, in which hyaluronidase is doubtless inactivated. But, like several others, I have also seen granulosa cells of ova in Ringer-Locke's solution leave their fellows

while vigorous spermatozoa thrash among them. I had thought that while in culture in vitro, and so possibly in vivo in the tube, granulosa cells died because of separation from the follicular lining and, by resultant proteolysis, lost their cytoplasmic connections, thus dissolving the intercellular matrix by their own degradation products, and so easing their removal by motile sperm. And indeed this may be at least one of the means by which the ovum is stripped. But there is hyaluronidase in or on human sperm,⁴¹ and only a little is needed to dismember hyaluronic acid. This method, then, may be either an essential or merely an adjunctive one. The question is important, for on the answer, as determined by more extensive, controlled experimentation, depends the significance in human fertilization of the presence or of the amount of hyaluronidase in or on the spermatozoa.

Attempts to fertilize mammalian eggs in vitro have been numerous, and successes exceedingly few, and in only two species, the rabbit⁴² and the human being,⁴³ and in only one medium, Ringer-Locke's solution. Is there a substance present in tubal fluid and absent in culture mediums that facilitates fertilization? In some of the invertebrates whose eggs form a fertilization membrane after the entrance of one sperm, the enzyme "fertilizin" is postulated as on, and perhaps in, the egg.³⁰ This reacts as an antigen to the first sperm that makes contact so as to form a substance that makes impossible the entrance of other sperm heads. Is there present in blood serum and some other body fluids, including semen, an antistubstance that makes penetration of the vitelline membrane by even one sperm, or engrossment of the sperm by the vitellus, impossible? Pincus,⁴² working with rabbit ova, and Menkin and Rock,⁴³ working with human ova, were unable to cause recognizable fertilization of even denuded eggs in blood serum.

* * *

It must be concluded from the foregoing discussion that much remains to be learned about how human beings reproduce. This ignorance is not fatal, for fortunately the intricate process does not require carefully executed managerial control — that is, when the delicately adjusted and integrated mechanism functions normally. Furthermore, perfection in each unit is not always required for in many details there is a fortunate leeway of error. On the other hand, when an apparently healthy copulating couple fail to reproduce, knowledge of required physiology is necessary for success. Knowledge is also requisite for faultless and harmless prevention of conception, which human reason clearly manifests is an indispensable factor for the health, wholesomeness and progress of human society. Intensive research will bring rich rewards that will greatly facilitate the elevation of fallen man.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 35201

PRESENTATION OF CASE

First admission A twenty-one-year-old barber was admitted to the hospital complaining of crampy abdominal pain.

Three years before admission the first episode of low abdominal cramps appeared. There was no obstipation or vomiting. He was hospitalized for two days. The second attack occurred twenty-seven months before entry. He was hospitalized, an appendectomy was performed. He was well until four months later, when nausea, vomiting and jaundice appeared without any severe abdominal pain. He was hospitalized for three weeks, at the end of which the jaundice had disappeared. Following discharge he began having episodes of crampy lower abdominal pain, with constipation for two or three days, which then subsided for symptom-free intervals of about a month, to be followed by similar episodes. There was no nausea or vomiting with these attacks. The attacks over the three-year interval had a persistent pattern. The cramps, definitely lower abdominal, were increased by ingestion of food. The symptoms were accentuated as the day progressed. A prodrome of "tightening up" in the lower abdomen preceded cramps. Constipation with the cramps was usually relieved by enemas. Between attacks the appetite was fair, there was no indigestion, the bowels moved daily, and there was no melena or hematemesis. One week before admission an attack recurred with the usual lower abdominal cramps, constipation and the inability to pass flatus. Several enemas helped a little, and mineral oil three days before entry gave him some loose movements. In the two days before admission there were no further bowel movements, nausea and vomiting appeared for the first time and persisted. He vomited solid foods but was able to retain liquids. The abdomen did not become distended.

Physical examination showed a thin, slightly dehydrated man in no distress. The chest was normal. Spasm of both rectus abdominal muscles was present. There was no tenderness or masses and

no distention. Occasional high-pitched peristaltic tinkles were heard. A well healed appendectomy scar was seen. Rectal examination was negative.

The blood pressure was 130 systolic, 70 diastolic. The white-cell count was 16,000. The hemoglobin was 14.8 gm. The urine was normal. The stools were repeatedly guaiac negative. The serum total protein was 7 gm. per 100 cc. The cephalin-flocculation test was ++ in twenty-four and forty-eight hours. The gastric contents were guaiac negative, and free acid was present. The sedimentation rate was 5 mm. in one hour. The blood Hinton test was negative.

A plain film of the abdomen and barium enemas demonstrated no abnormality. A gastrointestinal series, including small-bowel examination, was negative. The Graham test showed good concentration, and contraction after a fatty meal. No stones were seen. Proctoscopy and sigmoidoscopy showed no abnormality.

While in the hospital the patient was afebrile. On a soft diet and cathartics the symptoms decreased in severity. The white-cell count returned to normal. He was discharged on the tenth hospital day. A full diet supplemented by mineral oil and metamucil was prescribed.

Second admission (one week later) He re-entered the hospital with a recurrence of severe lower abdominal cramps and constipation of three days' duration. There was no change in the objective findings since discharge.

An operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. EDWARD HAMLIN, JR. This case seems unusual for one of these exercises in that there is a complete lack of red herrings or any positive information. I think it would be helpful to see the films.

DR. STANLEY M. WYMAN. There is very little to add to the written description. The plain film of the abdomen reveals no unusual soft-tissue shadows and no evidence of intestinal obstruction. I can see no definite stones. Films after the Graham test show no organic abnormality. The barium enema and the gastrointestinal series show, as far as I can see, a normal large bowel, stomach and duodenum, and on these two films taken at one and two hours, respectively, a normal-appearing jejunum and ileum.

DR. HAMLIN. That is no help either.

We have, then, to explain the cause of lower abdominal cramps that eventually required an operation and, in a young, apparently otherwise healthy person, had occurred intermittently and perhaps increasingly over a period of three years. One examiner, at least, had the opportunity of exploring the abdomen and removing the appendix, but apparently the cause of the present difficulty was not noted even though presumably the difficulty

had been present before. The episode of jaundice, we will do well to discard and call some form of infectious hepatitis because, at that time at least, the symptoms of which he had previously complained and of which he later complained apparently were in abeyance.

Lower abdominal, crampy pain usually means large-bowel involvement, and the causes of lower abdominal crampy pain as applied to large bowel would mean some degree of subacute intestinal obstruction. Volvulus is something that one should think of, but I certainly see nothing in the films that looks like volvulus, nor do I see anything that looks like subacute intestinal obstruction. There are many other possibilities in the large bowel. One can run through a list of them, only to say that the normal barium enema, negative proctoscopy and sigmoidoscopy should effectively rule them out. They are not necessarily ruled out by such procedures, but for our purposes we must assume that they were. Small-bowel difficulties can also cause crampy low abdominal pain. Usually, pain in the small bowel is referred to the region of the umbilicus, disease of the lower end of the ileum, however, may cause, as most of us have seen, pain referred to the lower abdomen. Since the roentgenologist has a far more difficult job to rule out disease in the small bowel than in the large bowel, and since proctoscopy and sigmoidoscopy do not reach that far, it would perhaps be politic to confine our attention to the lower small bowel. It would seem at least unusual to have to examine the intestinal tract any higher than that.

What other possibilities of subacute intestinal obstruction have we to consider? The description is certainly that of a low order of intestinal obstruction. What are the possibilities of such an obstruction existing in the face of no increase in distention noted on several occasions, and no increase of air in the small bowel as seen on x-ray study? The only evidence is the subjective impressions of the patients, and it was mentioned that occasional high-pitched peristaltic sounds were heard. Again, one can run through a long list of possible lesions. We can, however, restrict ourselves to a lesion that had existed for at least three years, which will rule out a good many conditions or make them at least much less likely. For my own sake, I cannot see the point of running through a long list except from a statistical point of view. Certain things can be ruled out or partially ruled out, such as lymphoma, which should have produced blood in the stools on some occasion, although it might have existed for three years. A lipoma or large polyp of the small bowel could produce such symptoms. I expect, however, over this period of time that some bleeding would have been noted at least microscopically. The one best entity that I can think of that would be chronic and that would produce very slowly increasing symptoms would be a constricting lesion

of the small bowel, which produced symptoms only when some intercurrent irritation of the bowel was present, and, of these, the best example that occurs to me is carcinoid.

DR JACOB LERMAN: The results of the barium enema need not rule out volvulus. The bowel could unwind in a few hours.

DR HAMLIN: Yes, but a redundancy of the sigmoidal loop is usually seen. Certainly I do not think one can rule out anything with the data as presented, but I think volvulus is unlikely.

DR ALFRED KRANES: Was the original appendectomy done here?

DR TRACY B. MALLORY: I think not.

DR HAMLIN: I should also mention Meckel's diverticulum as a possibility.

DR MALLORY: Dr. Ellis, you saw this man.

DR DANIEL S. ELLIS: Yes, but as Dr. Donaldson's patient. I saw him in consultation. He had been followed outside by one or two doctors, who had become desperate because of the recurrent attacks, and they sent him down here for surgery. I saw him and decided that the history was not very definite. I did not see him in an acute attack in the first hospital admission, and I was of the opinion that he probably did not have anything but "gas pains," but that if he did have something, Meckel's diverticulum was the most likely possibility. I was largely responsible for saying that he should not be operated on at the time of the first admission but that he should be sent home with definite rules to follow and that, if he continued to have pain, he should be explored even though we might not know at that time what he had. I thought it important to be absolutely sure in view of recurrent attacks that there was not something that might be cured by surgery if attacks continued. They did, and he was explored.

DR GORDON A. DONALDSON: The family physician was the only one who really knew what should next be done for this patient — and that was to be a diagnostic exploratory laparotomy. However, he had had the chance, as Dr. Ellis pointed out, to see him in an acute attack. During the first admission the patient had had no acute pain, so we did a proctoscopy and a sigmoidoscopy because the pattern of his pain pointed to the large bowel, as Dr. Hamlin has said, and we had a very good view of the large bowel both from proctoscopy and barium enema. It was low abdominal crampy pain, which we associate only with large-bowel lesions. The other point was that the patient was constipated and had been constipated for some time and had taken a high-carbohydrate diet, it was believed that he might have nothing other than constipation. Sure enough, he was home for only three days, long enough to become constipated again, when he appeared for the second admission. On two consecutive days he again had pain after eating. We

finally did an exploratory laparotomy as a diagnostic procedure

DR HAMLIN The implication is that we are descending the bowel. I cannot descend it with you though

CLINICAL DIAGNOSIS

Meckel's diverticulum?

DR HAMLIN'S DIAGNOSIS

Carcinoid of small bowel

Meckel's diverticulum?

ANATOMICAL DIAGNOSIS

Persistent omphalomesenteric duct, with focal ulceration, probably peptic

PATHOLOGICAL DISCUSSION

DR DONALDSON I would like to draw a diagram of the lesion. It was something I had not seen in an adult, although at the Children's Hospital it is seen occasionally. This is a lateral view of the abdomen, with the navel in the center, and this is a loop of small bowel. About 60 cm from the ileocecal valve (where it should be), there was a patent tube-like structure measuring 25 cm in length and 1 cm in diameter, running from the ileum to the umbilicus. There was a good deal of thickening near the umbilical end, and this was important in view of the symptoms.

DR MALLORY This tube, which was resected, was lined with intestinal mucosa of the small-bowel type. At one spot was an area of ulceration, which looked very characteristic of peptic ulcer, although in several sections we were not able to identify any gastric endothelium. I think probably it was present, and we missed it in picking out blocks for sectioning. The diagnosis, of course, is obvious — a persistent omphalomesenteric duct, which is much less common than the usual Meckel diverticulum. Projecting a short distance from the intestine. The origin of both is similar, of course.

CASE 35202

PRESENTATION OF CASE

A seventy-four-year-old man was admitted to the hospital because of abdominal pain of three days' duration.

The pain began suddenly following the ingestion of a small amount of food. It was severe, was

localized to the right lower quadrant and came in waves. There was associated nausea, and dark-green material was vomited. The pain persisted with slight diminution in severity. He had one stool and passed gas by rectum. The patient had always been constipated and took laxatives frequently. Several times recently he had noted tarry stools. Seven years before entry an acutely inflamed appendix had been removed, and a wound abscess had complicated recovery. Three years later a defect in the appendectomy scar and a right inguinal hernia were repaired. A year and a half before admission the patient had five or six episodes of severe epigastric pain. Following one of these episodes he was admitted to another hospital with vomiting and abdominal distention. A serum amylase of 500 units per 100 cc was found. A cholecystectomy was performed. The gall bladder contained many small stones, and the common duct was large and much thickened but contained no stones. The pancreas appeared to be thickened, but no areas of fat were visible. He recovered uneventfully and was well until four months before entry, when he was again hospitalized with a picture of intestinal obstruction. The serum amylase again was elevated. There was prompt recovery on conservative therapy. Guaiac tests on the stools were 0 to ++++ on several occasions. A barium enema showed no abnormality of the colon. He was readmitted to the hospital two weeks later when he had a sudden onset of pain radiating across the abdomen. There were fever, leukocytosis and an elevated serum amylase. On the sixth hospital day he felt something "give away" in his abdomen, and he was immediately relieved. A gastrointestinal series showed a small hiatus hernia. The stomach and esophagus were normal. The duodenal cap was intrinsically normal, but the bulb, although normal in size, showed an abnormally smooth contour to the inner loop, questionably encircling a mass. Also, a questionable filling defect of the mid-transverse colon, not previously seen, was noted on barium enema.

Four weeks before entry "operation for strangulated umbilical hernia" was performed at another hospital. He remained well until the present episode.

On physical examination the chest was emphysematous. There was a Grade II, precordial systolic blow. The abdomen was distended, more so on the right, and was moderately tympanic.

Tenderness and spasm were present over the entire abdomen, most marked in the right upper quadrant, where a large, smooth, tender mass, 15 to 18 cm in diameter, was felt. The mass seemed to be continuous with the liver. Peristalsis was diminished. Rectal examination was negative except for an enlarged prostate.

The temperature was normal.

The urine specific gravity was 1.017, a trace of sugar was present, and the test for albumin was ++. Many granular casts and 5 pus cells per high-power field were found in the sediment, which gave a ++ test for bacteria. Examination of the blood showed a hemoglobin of 13.8 gm. The white-cell count was 12,000, with 82 per cent neutrophils. The nonprotein nitrogen was 66 mg per 100 cc. The van den Bergh reaction was 0.8 mg per 100 cc direct and 1.4 mg indirect. The stools were guaiac negative. A plain film of the abdomen showed no obstruction.

Auricular fibrillation was noted a few hours after admission. The pain, vomiting and distention persisted. On the second hospital day one observer felt a mass in the right upper quadrant, which was believed to be attached to the liver. On the third hospital day the patient suddenly cried out with pain and vomited, and the abdomen became rigid and silent. Preparations for operation were made. As anesthesia was given, the patient suddenly became pulseless, and respirations soon ceased.

DIFFERENTIAL DIAGNOSIS

DR RICHARD WARREN: It is significant that the pain was in the right lower quadrant. It is important to note that the sequence of events began a year and a half before entry. I believe that the seven-year and three-year episodes can be put down as separate diseases or separate episodes in this man's history.

May we see the x-ray films?

DR STANLEY M. WYMAN: This is the only film available. It is a plain film of the abdomen taken after admission and shows the gas-filled cecum, the transverse colon and the splenic flexure. I cannot see the descending colon or rectum. There are no dilated loops of small bowel and no unusual areas of calcification.

DR WARREN: Is there any evidence of fluid or gas?

DR WYMAN: I cannot be sure that there is free fluid or gas in the abdominal cavity. The film was

taken with the patient in an upright position. I am not much help.

DR WARREN: In discussion of this case I would first like to take up the point of whether or not the patient had something new on this admission or whether what he had was a direct extension of the previous symptomatology. When he entered this hospital the trouble was in the right lower quadrant for the first time. A serum amylase was not done so it raises a little doubt whether the patient had something new or whether it was a continuation of the old symptoms. However, the discussion of the case can best be centered around the question of whether or not he had pancreatitis. I would like to point out the things in favor of pancreatitis and those against it. The pain came on after the ingestion of food. Pancreatitis is supposed to come on after dietary indiscretion, such as overeating of food. This one came on with the eating of food in small quantities. Pain in the epigastrium on the previous admission is in favor of it also. Above all we have the operative findings. The gall bladder was removed, the pancreas was found to be thick, and there was disease of the common duct. They are the most cogent features in the past history. The x-ray films showing extrinsic pressure on the duodenum and transverse colon are in favor of pancreatitis, as is the presence of a tender inflammatory mass in the upper abdomen. The patient did not have much infection and the low white-cell count and normal temperature could be perfectly consistent with pancreatitis. The polymorphonuclear ratio is not recorded, nor is the pulse.

DR BENJAMIN CASTLEMAN: The patient was in for only three days on the last admission. The pulse was 80 on admission, but went up later to 100.

DR WARREN: That does not mean a great deal except that he did not have an overwhelming infection. Finally, the elevated serum amylase, which was determined at the other hospital and repeated here, is overwhelming evidence in favor of pancreatic necrosis.

What do we have against pancreatitis or pancreatic disease? We have a history of tarry stools. We have a ++++ guaiac test on the stool on the previous admission. This might be thought to be some evidence against pancreatitis. However, I believe that it is consistent with it, particularly an inflammatory lesion with presumably enough congestion of the gastrointestinal region to cause bleeding. I have recently seen a patient who had

pancreatitis who was a problem in differential diagnosis because of the fact that he had tarry stools. Because of the blood in the stools many people thought that it was not consistent with pancreatitis. I am sure that it is. I cannot explain right-lower-quadrant pain in pancreatitis. The absence of back pain in pancreatitis of this degree is very unusual. The abstract does not say that it was absent, it merely does not mention it. The mass on the right side of the abdomen is unusual for pancreatitis. An inflammatory mass in pancreatic necrosis is most often in the midline or on the left in my experience. The absence of fat necrosis at the preceding operation throws a little doubt on the diagnosis. How far fat necrosis was looked for, I do not know. Fat necrosis in pancreatitis is classically behind the pancreas in the retroperitoneal area below the transverse colon. We are not told whether or not that area was inspected.

What else do we consider in differential diagnosis besides pancreatitis? The question of intestinal obstruction is brought up often in the history. The patient had previously been operated on for inguinal hernia, which makes me think of intestinal obstruction. I believe the x-ray examination rules out any significant degree of small-bowel obstruction. The fact that he passed gas and had a bowel movement during the three days of his illness is also against it. Peritonitis from perforation of a gastroduodenal lesion cannot be ruled out. He had a gastrointestinal series three months previously. Could some other viscus have perforated? The colon, possibly. In view of the history I do not believe that is likely.

How about the possibility of a vascular accident? Auricular fibrillation was noted. If we are going to assume a vascular accident, we must assume that he had something within the abdomen. He could not possibly have had repeated emboli to this region for a year and a half. Could he have had thrombosis of the celiac axis or the splenic artery? That might explain the final episode, but certainly it could not explain the long-standing history. The mass was always recorded as being contiguous with the liver. What condition in the liver could cause a mass of this nature? Could the patient have had a pylephlebitis coming from pancreatitis and a large abscess perforating from the liver into the right gutter? That is unlikely, I think. Cancer of the pancreas or of the bile duct in the

absence of jaundice is unlikely. As far as I am concerned I can make no other diagnosis than that of acute pancreatitis with abscess. I believe that death was due to rupture of this abscess into the peritoneal cavity. Presumably, the marked degree of collapse was due to the liberation of tryptic ferments from the abscess into the peritoneal cavity.

DR SEDGWICK MEAD Dr Warren, do you have any explanation for the episode when the patient felt "something give way" and then felt better?

DR WARREN I purposely skipped over that because I could not explain it. That is in favor of intestinal obstruction but there are so many other things in favor of pancreatitis here that I really must make that diagnosis.

CLINICAL DIAGNOSES

Metastatic carcinoma

Perforated viscus

DR WARREN'S DIAGNOSIS

Acute pancreatitis, with abscess formation and rupture into peritoneal cavity

ANATOMICAL DIAGNOSES

Pancreatitis, acute and chronic, with pseudocyst formation

Erosion of superior pancreaticoduodenal artery

Hematoperitoneum, severe

Squamous-cell metaplasia of pancreatic ducts

Adenomatous polyp of colon

PATHOLOGICAL DISCUSSION

DR CASTLEMAN When the abdominal cavity was opened the first thing that the prosector found was a large mass of blood clot in the right upper quadrant, going under the liver as well as over it. Most of this blood was old, but there was also a great deal of fresh blood, some of which was not clotted. It was estimated as being over a liter. I think we can assume that that was the immediate cause of death—that is, exsanguination into the abdominal cavity.

Further exploration revealed blood in other parts of the abdominal cavity, fresh rather than old. This blood was coming from a large cyst, which involved the entire head of the pancreas, or at least

involved the region where the head of the pancreas should be. This cyst was about 12 cm. in diameter, and on its superior aspect was a hole from which blood apparently had escaped into the abdominal cavity. When this cyst was opened the lining was found to be shaggy and covered with fibrin and old blood. On the posterior aspect of this cyst there was a small blood clot that blocked the opening of a large artery, which was found to be the main superior pancreaticoduodenal artery. We have, then, erosion of an artery into this cyst and rupture of the cyst superiorly into the right-upper-quadrant region and the abdominal cavity. There was also another smaller cyst just to the left, which involved part of the body of the pancreas. The tail and rest of the body of the pancreas were firm and on sectioning showed the normal lobular architecture. The pancreatic duct was dissected beginning at the tail and found to end abruptly in scar tissue just about where the cyst began, when dissected from the ampulla, it was patent down to the same spot behind the cyst. So there was obliteration of the pancreatic duct in its mid-portion for a distance of 12 cm. Sections of the cyst showed just fibrous tissue without any epithelium. Sections of the body and tail of the pancreas showed a mild inflammatory reaction, mostly monocytes and lymphocytes and a few polymorphonuclears. Most of the pancreas was fairly intact. The ducts, however, showed a very severe degree of squamous-cell meta-

plasia, which according to Rich* may be a factor in the cause of pancreatitis — that is, the heaped-up squamous cells blocked the smaller ducts allowing for seepage of the ferments into the parenchyma to produce pancreatitis. Whether that was the primary disease here or a secondary change due to the block caused by the cyst, I do not know. With long-standing obstruction in any duct, squamous-cell metaplasia may develop. I believe these cysts originated from previous necrosis of the pancreas and were "so-called" pseudocysts of the pancreas rather than true neoplasm. When the pseudocysts appeared, I do not know. Certainly they were not present a year and a half previously, when the patient was operated on by Dr. McKittrick, who examined the pancreas very carefully and found nothing but a thickened pancreas and no fat necrosis. We found fat necrosis all over the abdomen. It is possible that what "gave way" was one of the pseudocysts, which relieved the tension in the pancreas.

DR. WARREN: There was no suppuration in the pancreas itself, just two hemorrhagic pseudocysts?

DR. CASTLEMAN: That is right.

DR. WARREN: Did the pancreatic duct communicate with the cyst?

DR. CASTLEMAN: No. The patient also had an adenomatous polyp in the colon which may account for the positive guaiac test in the stools.

*Rich, A. R. and Duff, G. L. Experimental and pathological studies on pathogenesis of acute hemorrhagic pancreatitis. *Bull. Johns Hopkins Hosp.* 58:212-259, 1936.

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A NEW VIRUS DISEASE

DURING the past few years several new nonbacterial infections apparently transmitted from animals have been described in human beings. Notable among respiratory infections have been psittacosis (ornithosis), which is transmitted from birds, and Q fever, apparently acquired from cattle. Evidence that a new virus disease of fowls, which has recently been recognized as highly prevalent in the United States, may be transmitted to human beings and may be spreading in some parts of this country has recently been presented by workers of the United States Public Health Service*.

In 1926, a highly infectious and fatal disease of fowls was recognized in the Dutch East Indies

and at about the same time at Newcastle-on-Tyne. In England a filter-passing agent, designated as Newcastle disease virus was isolated from infected birds in the following year. Similar outbreaks were soon described from various parts of the world outside the United States, but it was not until 1941 that a disease of chickens was recognized in California under the name of avian pneumoencephalitis. The disease in fowl is usually characterized by neurologic symptoms in immature birds, whereas respiratory manifestations predominate in the adults. This disease was subsequently shown to be caused by a virus similar to the one that causes Newcastle disease. Systematic surveys subsequently demonstrated the presence of the disease in almost all parts of this country. It has therefore become of major importance to poultry men throughout the world.

Many groups of workers have studied the Newcastle disease virus. It has been found possible to propagate the virus in embryonated hens' eggs, and the infection has been transmitted to some laboratory animals by intracerebral inoculation. It is of interest that this virus has the ability to agglutinate chicken red cells just as the influenza and mumps viruses do. Although many workers have handled both the virus and infected fowl tissues, there have been very few reports of human infections. All the previously recorded human infections with this agent seemed to involve the eyes and had resulted from accidental laboratory infections.

Although the Newcastle disease virus was first recognized in California in 1941, it was not reported in the eastern states until 1944-1945, and it was at about this time that certain atypical cases of human infection began to appear in Tennessee. Furthermore, the disease in fowl was not described in Alabama and Tennessee until 1947, although it may have been present earlier, and apparently some human infections also began to appear in Alabama in 1948 or perhaps late in 1947.

Howitt, Bishop and Kissling, working in the virus laboratory of the Communicable Disease Center that the United States Public Health Service operates in Montgomery, Alabama, studied serums received in 1947-1948 from various groups

*Howitt, B. F., Bishop, L. K., and Kissling, R. E. Presence of neutralizing antibodies of Newcastle disease virus in human sera. *Am. J. Pub. Health* 38: 1263-1272, 1948.

of children in Alabama and Tennessee who had suffered from a mild and brief central-nervous-system infection that had left no sequelae. Some of the patients were thought to have some form of encephalitis, and others were considered as having nonparalytic poliomyelitis.

Because of a history of frequent association with chickens and the absence of antibodies for common neurotropic viruses, these workers did neutralization tests with these serums against the virus of pneumoencephalitis or Newcastle disease of fowl. Of 15 serums from children in Tennessee with this new clinical syndrome, 12 showed antibodies for the virus of Newcastle disease. One case of encephalitis and one with a poliomyelitis-like syndrome also had antibodies for this virus. Numerous other serums that had been obtained in previous years from children without this atypical syndrome were negative. Two chickens from the premises of one of the patients showed both the pathological lesions of Newcastle disease and the presence of neutralizing antibodies in the blood. Serums were also obtained from 10 human cases of a mild central-nervous-system syndrome in rural areas of Alabama, and 8 of these showed definite neutralizing antibodies for the virus of Newcastle disease, and chickens with similar antibodies were also found in association with several cases.

After work with the virus was started in the Montgomery laboratory, an acute influenza-like infection developed in 6 of the laboratory personnel. Antibodies in high titers against the virus of Newcastle disease were found in the serums of these 6 persons. In addition, antibodies were found in 4 of 11 serums from laboratory personnel without symptoms. Serums obtained from 19 people before the virus work began showed no such antibodies. However, the blood of 3 persons who had typical symptoms before they came to the laboratory also showed neutralizing antibodies for Newcastle disease, whereas neutralization tests were negative on serums obtained earlier from many children and adults who had not shown these atypical neurologic symptoms.

Although no virus has yet been isolated from any of the human cases in this country, Howitt and her co-workers believe that their evidence in-

dicates that the virus of Newcastle disease of fowls is probably the agent responsible for many of the atypical central-nervous-system infections that have been reported in man during the past few years. They also suggest that, as in fowl, the manifestations are neurologic in young persons and influenza-like in adults. They believe that the virus originating with fowls has probably spread to man, and their evidence suggests that in many cases there is a man-to-man, rather than fowl-to-man, dissemination of the disease.

NO HOLDS BARRED

THE Committee for the Nation's Health, in a characteristic release, continues its campaign of disparagement against the American Medical Association. Since the Association is the accepted agent of a large majority of the practicing physicians of the United States, who are currently expressing their approval of its present policies in a very tangible manner, this campaign has the effect of reflecting on their judgment.

The Committee for the Nation's Health, under the chairmanship of a former president of the Massachusetts Medical Society, scrutinizes in this release the relations between the American Medical Association and the National Physicians Committee, suggesting that the American Medical Association may be blowing both hot and cold. It happens that nothing particularly new has developed in these relations. Since the formation of the National Physicians Committee over ten years ago, it has had the general approval of the American Medical Association, and this general approval has at no time been withheld. Within a matter of months the objectives of the National Physicians Committee have also been approved by the Council of the Massachusetts Medical Society.

The National Physicians Committee, during the course of its activities, has made some palpable mistakes. So have the American Medical Association and the Congress of the United States and so have most, if not all, of the persons comprising our somewhat disturbed society, if given the opportunity. Even the Committee for the Nation's Health, granted a long enough rope and enough time, may some day be in error.

The Committee for the Nation's Health continues its allusions to the "slush fund" of the American Medical Association, employing suggestion as a substitute for evidence, it crows over the news that Whitaker and Baxter, in dutiful compliance with the law of the land, have registered as lobbyists. Congress, it may be hoped, will not be unduly disturbed over the implication that the profession of lobbying, which it has legally recognized, is somehow not respectable.

The physicians, at least, on the Committee for the Nation's Health, are aware that the profession to which they are devoted is under heavy fire. Regardless of whether, in their devotion, they believe that it requires a major operation or can recover through more conservative treatment, they must admit that the argument cannot be fairly settled with six shooters on one side of the table and water pistols on the other.

CORN FOR INSTANCE

NEWSPAPER headlines and magazine digest articles that keep the public informed concerning scientific progress make it hard for the family medical adviser to remain a jump ahead of his patients. For example, what is monosodium gluconate, is a diet of rice and pineapple juice "good for you", what about salt substitutes, does the television tube emit enough gamma rays to warrant concern over its possible harmful effects on the family, can oranges be bought to better advantage by the pound or the dozen, is painless childbirth possible without anesthesia, and, perennially, should canned foods always be immediately emptied into a dish when the tin is opened?

One might suppose that housewifely concern over the supposed dangers of canned foods had been completely quieted, now that perhaps three fourths of the food comes from tins and the younger generation has almost universally learned to prefer canned peas to the violently green fresh variety that seems to please their elders. But enough vague fear of what may happen to food left in the opened tin persists to impel the manufacturers of tin cans to publish accurately documented scientific information about the healthfulness of the products sold in their containers. These products are steri-

lized in the tin, which may or may not be lined with a coating of enamel, in any case no harmful interaction occurs between food and container, and the food is more apt to stay sterile and harmless if left in the clean open tin (provided it is kept cool and covered) than if placed in a dish of questionable sterility and left exposed. Eye appeal may be enhanced if the food is placed in an attractive bowl, but hygiene does not require the transfer.

HEALTH ACCESSORIES

BRITAIN'S bald heads of both sexes, according to a recent statement in *Newsweek*, will soon be demanding Government-financed wigs at the rate of 100,000 a year. The estimate has been made by the two dozen busy wigmakers currently engaged in supplying utility wigs, at \$40, and non-utility wigs, at \$50, for the Ministry of Health.

Two styles of wigs are furnished for men, full wigs or "sculpettes," and five for women. Each applicant is allowed two wigs at \$40, creating a possible demand that may cost the Government \$8,000,000 annually, in addition, cleaning and dressing the spare wig every two months (another Government obligation) will add \$400,000 to the bill.

Under other provisions of the National Health Act false teeth, hearing aids, trusses, electric wheel chairs and spectacles are supplied to a grateful public. November estimate of the Ministry of Health was that 1,700,000 pairs of glasses had already been issued. An applicant was unsuccessful, however, in procuring a free bottle of hair shampoo.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

HEFFERNAN — David A. Heffernan, M.D., of Brighton, died on April 18. He was in his sixty-ninth year.

Dr. Heffernan received his degree from Harvard Medical School in 1902. He was a member of the New England Otological and Laryngological Society and a fellow of the American Medical Association.

His widow survives.

SMITH — Lillian R. Smith, M.D., of Harwich, died on April 15. She was in her sixty-fourth year.

Dr. Smith received her degree from Tufts College Medical School in 1917. She was formerly director of Maternal Health and Child Hygiene in Michigan and was in charge of the Emergency Maternal and Infant Care Program in that state during World War II. She was a fellow of the American Academy of Pediatrics and the American Medical Association.

A sister survives.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

RHEUMATIC-FEVER FELLOWSHIPS

The United States Children's Bureau has made available through the Massachusetts Department of Public Health and the Harvard Medical School one fellowship in rheumatic fever at the House of the Good Samaritan of the Children's Medical Center, Boston, for the year beginning July 1, 1949.

Applicants should be interested in working eventually in the field of rheumatic fever in public health or in teaching, rather than in private practice.

Work under this fellowship will probably be acceptable for credit by the American Board of Internal Medicine or the American Board of Pediatrics.

Application should be made as soon as possible to Dr. Benedict F. Massell at the House of the Good Samaritan, 25 Binney Street, Boston 15 (telephone, BEacon 2-3002).

REPORTS OF RESEARCH PROJECTS IN PROGRESS

Division of Biologic Laboratories

In this division, field studies in medical students and Army personnel in collaboration with the staffs of various medical schools, hospitals and other groups in Greater Boston regarding diphtheria immunity in adults are continuing with the support of a Government contract, studies of immunity in diphtheria patients in collaboration with the staff of Boston City Hospital are still in progress, in the chemical and immunologic studies on purification of diphtheria toxoid, begun in 1944 and continuing to date, various methods have been employed, and recent results have produced a toxoid almost 100 per cent pure and considerably more potent than the starting material (studies are also under way on methods for more exact measurement of the potency of diphtheria toxoid), for the past five years a long-term study on the stability of biologic products has been in progress, directed toward elimination of unstable lots and discovery of stabilizing substances, studies of newly reported methods of rapid diagnosis of smallpox have been undertaken, for possible use in an emergency, in conjunction with the development of pertussis vaccine, studies have been instituted on the blood-cell clumping factor in pertussis cultures, on the toxic factor in culture supernatants and on other significant properties of pertussis preparations, about 1600 liters of outdated plasma have been fractionated, laboratory and clinical tests on albumin and gamma globulin prepared from this source having shown both fractions to be fully as effective as the products made from fresh plasma (this finding opens the way to a major and hitherto undeveloped field of blood fractions), under grants from Research Corporation totaling \$41,940 (July, 1945, to June, 1949, inclusive) a program for testing blood fractions made under license from the Cohn patents has been conducted and has included tests on numerous major and minor products, and assistance to miscellaneous studies.

Division of Cancer and Other Chronic Diseases

In this division, an effort is being made to evaluate detection-center activities, to measure screening by means of the seven danger signals and to ascertain the incidence of cancer among persons with and without any of the seven danger signals, a six-year evaluation of the cytology test for cancer, which is more than half completed, will answer many questions regarding procedures and will determine the value of the test itself, a study is underway showing environmental factors in relation to the length of life of patients after visiting a cancer clinic, in a long-term study on environmental factors in relation to the etiology of cancer one report is in the process of being published, and others are nearly ready (cancer of the breast, cervix and skin are being studied at present, a continuation project on familial aspects of cancer that has been in progress for several years embraces the possible etiologic effects of heredity, conjugal state, number of children and so forth, the accuracy of the death record in respect to certain chronic diseases is constantly under study and will continue until maximum results have been obtained (work has been done on heart disease, cancer, diabetes, nephritis, arteriosclerosis and rheumatism), since at present certain sites of cancer show an upward trend in death rate and others a downward trend, and still others are trendless, twenty sites are being watched, and future changes in their trends will be reported, the best mediums and the various channels for propaganda purposes, for creating awareness and for stimulating patients to action if symptoms of cancer appear are being evaluated.

Division of Communicable Diseases

In this division, a bacteriologist assigned to the Virus Laboratory at Harvard Medical School is working on the laboratory aspects of the diagnosis and epidemiology of poliomyelitis, a study to determine the feasibility of giving booster doses of diphtheria toxoid to high-school students is underway, records of all cases of typhoid fever reported since 1940 are being thoroughly analyzed, the titers of naturally occurring anti-A and anti-B isoimmune bodies in the serum of persons donating blood to the mobile blood bank are being studied, the presence, type and titer of Rh antibodies in the serums of Rh- persons who have received transfusions of blood not typed for the Rh factor are being investigated, studies directed toward improving the mediums and methods of culturing of tubercle and diphtheria bacilli and enteric pathogens are underway, and the laboratory, in co-operation with the Influenza Information Center, National Institute of Health, is performing serologic tests on blood specimens from persons suspected of having infections with either influenza A or B viruses.

Dental Division

Observations on the clinical effect of the use of a fluorinated dentifrice on the incidence of dental caries in 3000 school children are in their second year in two separate locations, fluorination of the water supply of two state schools is now in its third year of operation, and a yearly check on the incidence of dental caries is being kept by investigation of the rates of decayed, missing and filled teeth (nutritional studies are being included)

Food and Drug Division

The effects of the addition of water upon food value and keeping qualities of shucked clams by the various methods of washing, as practiced in clam-shucking plants, are being studied, new, sensitive, qualitative test for the detection of glycogen in horse meat is being investigated, the stearin derived from beef fat, horse fat and pork fat, or mixtures of these fats, is being identified microscopically, and the specific volumes of the hemi-cellulose content of soy flour in frankfurters is being determined, the analytical constants to determine genuine qualities of cider and other vinegar are being evaluated, the possibilities of a rapid sorting test for the initial separation of samples of enriched flour from those of unenriched flour are under investigation, the methods of identification of the newer synthetic narcotic drugs are being studied, a new, sensitive method for the detection of urea-formaldehyde sizing in garnetted clippings or shredded cloth is being developed, and analytical procedures for differentiation of new and second-hand bedding filling materials are being evaluated

Division of Maternal and Child Health

The activities of this division include performance of the Massachusetts hearing test (a successful and inexpensive adaptation of pure-tone-testing methods to large groups of children), a study of the relation of stereopsis to muscular co-ordination and educational adjustment of children, the Harvard pediatric study of the incidence of illness and the types and costs of pediatric care and the maternal-mortality study conducted by the Committee on Maternal Welfare of the Massachusetts Medical Society

Division of Sanitary Engineering

In this division the following matters are being investigated: trickling filters, with emphasis on rates of B O D removal, effects of recirculation, size of filter medium, oxygen requirements and physical design, disposal of trickling-filter effluents on intermittent sand filters, design and operation of septic tanks for small installations, subsurface disposal of septic-tank effluents, with emphasis on rates of application to particle size of soil, anaerobic digestion of sludge from sewage receiving phenol and formaldehyde wastes, aerobic biologic treatment

of aldehyde-bearing wastes resulting from the manufacture of synthetic resins, aerobic biologic treatment of the effluent from the primary treatment of wool scouring wastes with calcium chloride, with special reference to B O D and color removal, methods of treatment of waste dye liquors to remove color and B O D, methods of treatment of shellfish to reduce pollution load, investigation of new methods of analysis, preparation of samples, new mediums and use of enterococci as an indicator of pollution, methods of removal of iron and manganese from the public water supplies of Lowell, Billerica and Somerset, effect of long storage on color, chemical changes and reduction of bacterial load of water, effect of particle-size gradation of filtering mediums versus effective size for the filtration of water and sewage, use of cumene hydroperoxide for reduction of B O D in sewage and industrial wastes, in co-operation with the Federation of Sewage Works and United States Public Health Service, the effect of chrome salts on B O D and an improved method for grease determination, method of analysis of gases produced by the anaerobic digestion of sludge, method of determination of phenols, effects of storage and inhibitors on determinations of phenols in water, effectiveness of precoat type of diatomaceous earth filters for removal of bacteria and reduction of chlorine demand in swimming pools, effect of sodium hexametaphosphate on yellow brass pipe, quantitative determination of odors in the atmosphere, a rapid method for the determination of fluorides in water, use of sodium fluoride in water for the prevention of dental caries, and investigation of various commercial weed killers

Division of Tuberculosis

The Division is at present carrying three research programs in co-operation with the Children's Hospital, Massachusetts General Hospital and the Boston Floating Hospital, under a grant from the National Institute of Health, streptomycin treatment of children suffering from acute forms of tuberculosis, including particularly the use of streptomycin in tuberculous meningitis and miliary tuberculosis, a five-year co-operative study of BCG vaccination in student nurses and medical students by the Massachusetts Department of Public Health and the United States Public Health Service to determine the desirable preinoculation test with purified protein derivative and the optimum dosage of BCG vaccine, method of inoculation, duration of immunity and degree of protection conferred, and the study of hormonal changes in patients with carcinoma, both during and after therapy with sex hormones and related compounds, under a grant to the President and Fellows of Harvard College and Harvard School of Public Health for study from September 1, 1948, to August 31, 1949 (this work is being carried on in the laboratory of the

Department through the Pondville Cancer Hospital, where, in January, 1949, a new research laboratory for cancer, under the direction of a half-time director, was opened

Division of Venereal Diseases

This division is evaluating the penicillin treatment of gonorrhea and syphilis, the streptomycin treatment of granuloma inguinale in varying doses to determine the most effective dose and schedules, aureomycin treatment of lymphogranuloma venereum in selected cases, and a research project to find the most effective transport mediums for gonococcus cultures

MISCELLANY

PLASTIC SURGERY

Plastic surgery as a specialty has become well recognized. During the two world wars surgeons accumulated a wealth of experience in this field, and consequently the specialty has been greatly enlarged to the point where it is represented in organizations and publications. The newest periodical to be welcomed into the ranks of medical journalism is the *British Journal of Plastic Surgery*, inaugurated in 1948, under the editorship of A. M. Wallace, M.Sc., of the Department of Surgery of the University of Edinburgh. It is the official organ of the British Association of Plastic Surgeons. In 1946 the American group began the publication of *Plastic and Reconstructive Surgery* as the organ of the American Society of Plastic and Reconstructive Surgery, Incorporated. The typography and illustrative work of both journals are excellent.

CORRESPONDENCE

CARBON TETRACHLORIDE AND AZOTEMIA

To the Editor In the April 7 issue of the *Journal* appears a comment by Dr. Jacob J. Silverman, of Staten Island, New York. Replying to this comment, I should give the following facts:

The patient concerned in the article on extrarenal azotemia, which appeared in the January 20 issue of the *Journal*, did indeed work in a rubber factory, and the question of any exposure to noxious agents at work was carefully considered. Not only was there communication with the factory physician about whether the patient had been exposed to noxious agents, but also one of the consultants who saw this patient was an authority on industrial diseases, and was asked to see the patient with this point particularly in mind. We were not able to obtain any evidence that he had used carbon tetrachloride or other noxious agents, and we believed that this possibility was excluded as far as possible.

JAMES H. TOWNSEND, M.D.

Mount Auburn Hospital
Cambridge, Massachusetts

SKIN THERMOMETERS AVAILABLE

To the Editor In the April 7 issue of the *Journal* (on Page 587) Dr. John B. Sears, in speaking of mercurial-type skin thermometers, states "I have found none like it manufactured in this country."

A little less than two years ago I purchased a mercurial-type skin thermometer manufactured by, "RASCHER AND BETZOLD, INCORPORATED," Chicago, Illinois. This thermometer is most satisfactory, and the price is very reasonable. I believe that any surgical supply house could order it for physicians desiring one.

ROBERT J. FERGUSON, M.D.

Ashland, Ohio

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Metabolic Brain Diseases and Their Treatment in Military and Civilian Practice By G. Tayleur Stockings, M.B., D.P.M. 8°, cloth, 262 pp. Baltimore: Williams and Wilkins Company, 1947. \$4.50.

Peripheral Vascular Diseases: Diagnosis and treatment By David W. Kramer, M.D., associate professor of medicine, Jefferson Medical College, assistant physician, Jefferson Hospital, chief clinical assistant, Vascular Clinic, Jefferson Hospital, visiting physician, Medical Division, and consultant on peripheral vascular disorders, Philadelphia General Hospital, attending physician, Metabolic Division, and chief of Diabetic Clinic, Jewish Hospital, attending physician and physician-in-charge, Department of Metabolic and Peripheral Vascular Disorders, St. Luke's and Children's Medical Center, and metabolist to Eagleville Sanatorium. With a foreword by Edward L. Bortz, M.D. 8°, cloth, 620 pp., with 157 illustrations. Philadelphia: F. A. Davis Company, 1948. \$8.00.

NOTICES

NEW ENGLAND DIABETES ASSOCIATION

The annual meeting of the New England Diabetes Association will be held in Thayer Hall, City Hospital, Worcester, Massachusetts, on Monday, May 23, at 4 p.m.

CLINICAL PROGRAM

Neuropsychiatric Aspects of Diabetes Dr. Foster L. Vibber
Potential Diabetes Dr. Joseph A. Lundy
Necrotizing Papillitis in Diabetes Dr. Edward F. Ramsdell
Pathology of Necrotizing Papillitis Dr. Raymond H. Goodale
Experience with Diabetic Coma at Worcester City Hospital Dr. Albert E. Hall
Optimism and Diabetes Dr. George Ballantyne

The clinical program will be preceded by the annual business meeting including the election of officers and four directors. This meeting is planned in conjunction with the annual meeting of the Massachusetts Medical Society, May 23 to 26. The meeting will be completed in time so that councilors of the Massachusetts Medical Society can attend the Cotting supper at 6:00 p.m.

AMERICAN SOCIETY OF ELECTROENCEPHALOGRAPHY

The annual meeting of the American Society of Electroencephalography will be held at Chalfonte-Haddon Hall Hotel, Atlantic City, on Saturday, June 11 and Sunday, June 12. The meeting will begin at 10 a.m. on Saturday, and there will be a dinner for members and their guests which ladies may attend, on Saturday night at the Chalfonte-Haddon Hall Hotel. On Sunday morning there will be a joint meeting with the American League Against Epilepsy, consisting of a symposium on corticothalamic circuits. On Sunday afternoon the American League Against Epilepsy will hold the remainder of their meeting, to which members of the American Electroencephalographic Society are invited.

The business meeting of the Society, open only to members, will be held on Monday, June 13.

AMERICAN NEUROLOGICAL ASSOCIATION

The annual meeting of the American Neurological Association will be held in Atlantic City, New Jersey, on June 13, 14 and 15, with headquarters at Chalfonte-Haddon Hall.

(Notices concluded on page xiii)

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THE SHATTUCK LECTURE*

La Médecine du Coeur

PAUL D. WHITE, M.D.†

BOSTON

IN 1806 there was published at Lyon in France by Mark Anthony Petit an essay entitled "La Médecine du Coeur," literally translated medicine of the heart but actually signifying not cardiology but medicine *from* the heart — that is, benevolence in the practice of medicine. It was composed of four parts written as poetry and presented as such before the Academy of Lyon, the first in 1800 on the difficulties and disappointments connected with the profession of medicine, the second in 1801 on trust in the physician, the third in 1802 on gratitude toward physicians, and the fourth in 1805 on pain. Petit was surgeon-in-chief of the Hôtel Dieu in Lyon, professor in the university and member of the Academy, there and of the society of professors of the medical schools of Paris, Brussels, Antwerp, Bordeaux, Nîmes, Marseille, Avignon, Grenoble and of Montpellier, where he had himself studied medicine. Nearly one hundred and fifty years have elapsed since these notable writings, but their truth and appeal endure and I have selected them as a text for the Shattuck Lecture of which I am sure Dr Shattuck would have approved. It is of interest that George Cheyne Shattuck was himself a student at Dartmouth Medical School during the early years of the nineteenth century at the very time that Petit was delivering his essays. In fact, Shattuck received his M.B. at Dartmouth in 1806. He was president of the Massachusetts Medical Society from 1836 to 1840 and delivered the annual discourse in 1828. He established the Shattuck Professorship of Pathological Anatomy at Harvard Medical School in 1853. At the time of his death in 1854 his will established this lectureship, which was called by his name.

I shall discuss the subject of *médecine du coeur* from four viewpoints, which at first sight may seem quite unrelated but which actually are closely interwoven and together present the picture of the

physician's position as a whole in the world of our day. All four subdivisions have been topics for addresses and lectures concerning the medical profession in the past, including Shattuck lectures themselves, but they have not, so far as I know, been correlated to give the complete picture. These four parts of the whole are in sequence: first, the individual doctor-patient relationship, secondly, the position of the physician in his community, thirdly, the national problem, and fourthly, the international or worldwide scope of medicine. Some would have it that in all these relationships a simple detached so-called "scientific" attitude should prevail, as from an "ivory tower," devoid of *médecine du coeur*, but those of us who have observed the actions of mankind during a generation are aware of the actual failure to apply science in such an attitude. So long as man is an emotional animal with a "heart," one must act truly scientifically — that is, with knowledge and wisdom — in recognizing that fact and in dealing with medical problems accordingly. I have long been impatient with the distinction so commonly raised separating the science from the art of medicine, they are both essential parts of one whole so far as the actual practice of medicine is concerned, embodying the know-how to deal with man himself as well as with his fellows of a lower order such as the bacteria that prey on him or help him. After all, science literally means knowledge based on accurate observation, and art is simply the skillful and scientific application of such knowledge, they are inseparable and should be taught as such.

It is so obvious to those of us who have been practicing medicine privately that our patients should be our friends that we do not often stop to ask the question, "Why?" The statement may seem trite to some, but to the beginner and to the skeptic it is well to pause a moment to present some of the answers. The first of all is in establishing more easily an accurate diagnosis. In my own field and in most other fields of medicine the diagnosis is in large part dependent on an adequate history

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†Clinical professor of medicine, Harvard Medical School; consultant in medicine, Massachusetts General Hospital; executive director, National Advisory Heart Council.

of the present illness, past troubles, family history, and social and business relationships. The sooner one establishes a sympathetic and friendly relationship with one's patient the sooner will one obtain the necessary information from all the story that can be told, any minor portion of the patient's account, sometimes in the form of a confession, may be vastly more important than all the laboratory tests in the world and may save not only time and money, but even misery and death themselves. A few years ago I gave an address to the McGill medical students entitled "The Patient Advises the Doctor," and to obtain such advice I asked some of my own private patients and also patients in the hospital wards to write to me what they thought would be worth telling young men and women who would soon be doctors themselves. I received many interesting and helpful replies, one of which was from Miss Mary Ellen Chase, professor of English literature at Smith College, whose essay inspired us to invite her to give the address at the annual banquet before this society a year ago. A letter to me from one of the ward patients at the Massachusetts General Hospital stated that she had so much friendship for her doctor that she would tell him even more than she would tell her priest. Such telling can contain invaluable information of strictly medical importance.

A second reason for establishing a friendship with one's patient is to ensure better treatment. Not infrequently necessary therapy is difficult, time consuming or expensive, and therefore likely to be neglected or postponed if impersonally prescribed by the physician. One might say "All very well, if the patient does not carry out the doctor's advice, whose fault is it? The patient's, of course." I deny that, except in rare instances in which one is dealing with persons of the lowest order of intelligence or who are mentally unsound, and even then the doctor should have recourse to some arrangement, public or private, which may more adequately deal with such persons than can the doctor himself with the limited time and resources at his disposal. In general, then, it is the doctor's fault if he cannot induce the patient or his family to carry out the necessary treatment, often the importance of establishing an initial friendship here becomes obvious.

The value of a clear and friendly explanation of one's diagnosis to the patient himself was well and forcefully stated by Petit more than a hundred years before it was appreciated by the medical profession in general, in fact, it is still frequently neglected even in these advanced and enlightened days. Petit wrote

When a patient asks us about the nature of his illness, we should not, like an oracle, reply in obscure terms and proclaim the ridiculous pretention of science in speaking only its language. The art of rendering oneself intelligible applies to all, and since it is one of the best means of persua-

sion, it should be one of the very first studies of the physician and medical student.

A third scientific reason for *la médecine du cœur* as it affects the private or individual patient is in the accretion of new knowledge. The co-operation of the patient in special investigations of symptoms, signs, mechanisms of disease that involve physiologic and biochemical procedures, prognosis, and therapy may be of inestimable value in the advance of medicine. Such co-operation is much more likely to come from a friend. For example, one of our recent studies has involved the follow-up records of 173 private patients of my own who consulted me over twenty years ago for neurocirculatory asthenia — all but 2 have been traced and one of these lost persons should be discovered before long, since she was a one-time volunteer in the Social Service Department of the Massachusetts General Hospital. Such a high percentage of success in follow-up study is less likely when one is dealing with case numbers and not with one's own friends. Also, post-mortem examinations are still of much value in adding to our medical knowledge, the families of patients of ours who have also been our friends are much more likely than the families of "cases" to permit such autopsies if we but take the trouble to ask for them.

A fourth reason for establishing a good doctor-patient relationship is for teaching purposes. Some of the most important lessons that I have been able to present in my teaching to both undergraduates and graduates of medicine have been made possible because some of my most articulate patients, who have taken an active part in the teaching of my students individually, in small groups, or even in large amphitheater clinics, have been warm friends of mine.

And, finally, there is a great personal satisfaction and joy in the establishment of human friendships, not wholly definable, both for the doctor and, I am sure, for his patients. This human relationship is doubtless a potent reason for attracting many to the profession of medicine as to religious ministries. There is something here that we doctors prize and for which we should be grateful, something that is sacrificed by those who deal largely with inanimate nature, or even with growing things in the vegetable and animal kingdoms that lack the intelligence and soul of man himself.

With this introduction of the role played by *la médecine du cœur* in the doctor-patient relationship that makes up the vast majority of the functions of the physician in the world, let me go on now to the place of the doctor in his community. Actually he holds his honored place locally because he is medical adviser and friend of many of his neighbors and of other citizens of his community and their families. Often he is himself the leading citizen of his village or town, and I have prized among my own friends physicians, mostly family doc-

tors, whose help was sought not only to diagnose and to treat disease among their patients but also to decide about the daily problems of the community, whether they concerned the public health or the schools, the church or even the roads. My own father, a family physician, was such a person, a deacon in his church, a teacher and an active man in the good works of his environment, great compensations, to be sure, for his hard and exacting life. At one time when he was ill and I was a hospital intern off duty for a few days I made rounds for him and quickly discovered that strictly medical advice played only a partial role in what was expected of him.

Many doctors have served on boards of health, school boards, lay councils of the church, and even governing boards of institutions and civic bodies, but as a rule they are too busy and must burn the midnight oil even to do their ordinary doctoring. It is at considerable sacrifice that they can do more, and not a few physicians have fallen victim to the demands that have been made upon them. They have practiced a benevolence (*médecine du cœur*) far beyond their strength, and I would here and now put in a plea not only to the doctors themselves but also to their communities to help to spare them for longer and greater usefulness than has been the lot of the majority of the doctors in the past.

Since the days of Hippocrates it has apparently been the tradition in medicine for the doctor to overwork and to be himself a sacrifice. It is expected of him, somehow, whether he be general practitioner, specialist, teacher, administrator or research worker. It may quite possibly have been a noble tradition, but often it has been too noble and unreasonable. There are some signs of improvement in progress in this respect. For example, nowadays, it is common for the young doctor or indeed even for the medical student to marry and to begin to raise a family, doubtless fostered in part by World War II but also by a saner public opinion, which in my day frowned on such doings until we were well established medically after completing our hospital residencies. Perhaps likewise it will be possible more and more by the establishment of group practice and convenient substitutions to give doctors adequate vacations and time off at night so that they will not be constantly on the job. The communities as well as the doctors themselves should see that this is done and that the doctor be treated as a human being and not as a machine. The opposite evil of the establishment of an eight-hour day for all physicians is equally to be avoided. Medicine is not a trade so to be arranged, but there should be a happy mean between these two extremes.

And last but not least the doctor's family must be treated with more respect than customarily in the past. Too often wife and children are disappointed in their plans because of the exigencies

of medical practice or research — some of this cannot be helped, but much of it can by better organization and by sharing of work, not in the form of socialized medicine with its threat to the all-important doctor-patient relationship but by simpler plans developed by the doctors themselves with the help of their respective communities.

There is another point of importance with respect to the doctor in his community, and that concerns his relationship with his medical colleagues. Great variations exist in such relationships from the friendliest co-operation to the bitterest hostility, fortunately the former situation holds most often. In Massachusetts we have been fortunate in inheriting and in maintaining a tradition of a friendly medical atmosphere. I would herewith pay tribute to the many physicians in Boston and throughout the State for their kindness and help to me, both personally, in my practice, and in my clinical research. My colleagues working in other hospitals in my field have invariably contributed data about cases, even from their private practice, to aid me in some study or other and have also given me their helpful advice and encouragement. Thus I would acknowledge my own debt and at the same time plead for more *médecine du cœur* from the doctor to his colleagues and from the community to its doctors.

The third phase of my subject deals with *médecine du cœur* for the nation. Here the public health is the main problem to be dealt with by both public and private enterprise. It is here too that I would plead for more understanding and co-operation between our Government administration on the one hand and the American Medical Association and its component parts in every state on the other. With a benevolent (*la médecine du cœur*) attitude to public-health problems of the nation, which is characteristic of each of these bodies, there should be no real conflict between them. Ample and friendly discussions should solve the difficulties that do exist. There is no need to enter into acrimonious dispute, which in the past has sometimes been based on personal prejudices and false pride.

It is obvious to us all that in the field of our own public health certain facts exist. In the first place, tremendous strides in medical knowledge by research have been made in this country during the past generation, more than in all the centuries of the past, and this has been in largest part under the stimulus, guidance and support of private enterprise in medical schools, hospitals and foundations throughout the nation. But it is now equally true that we are but at the beginning of our knowledge of the pathogenesis and mechanism of disease processes and of their adequate treatment and prevention. There remains much more still to be done than has been done in the past. Private resources, important though they still be, are inadequate for the job. Public aid, largely through

the new developments in the United States Public Health Service, can very wisely supplement the private resources for medical research. Not only is this necessary financially but the public wants and is now demanding a stake in medical research, and with increased interest and appreciation of the need and prospects for the future, they too wish to help. The greater number of trained research workers that can be put on the job with adequate facilities, the sooner we shall have answers to vital and important problems of public health such as cancer, or rheumatic fever, high blood pressure and coronary atherosclerosis, in which I happen to be personally interested and to help solve which the National Heart Institute was set up by an act of Congress last June. It was my conviction that public and private enterprise should join to fill this vital need, and that was why I enlisted part time in the work of the National Heart Institute and National Advisory Heart Council while continuing my private practice in cardiovascular disease. My experience to date, I might add, has been most encouraging—I have found my colleagues of the Public Health Service engaged in this work and my fellow private citizens on the Council most able, honorable, diligent and co-operative. *Médecine du coeur* has been constantly in evidence in all our deliberations and practice. I might add that it is these public officials themselves, medical and non-medical, who have constantly expressed and practiced a jealous protection for private enterprise and a liberal attitude toward private medical endeavor in research and teaching.

A second obvious fact that indicates the need of a liberal national support of medical endeavor in this country is the plight of the medical schools themselves. Both private and state schools require a large share of the resources of the universities throughout the country, so much so that the presidents themselves have been worried. Medical teaching is vital to the national health. Not only must we continue the high standards of the present day but also we must add appreciably to the output of new medical graduates. There are not enough doctors in the whole country as yet to meet all the demands. Since that is so I would plead for the admission to this country and for their distribution where most needed of several hundred able physicians still classed in Europe as displaced persons. Dr Burgess, of Providence, has well spoken in their behalf and incidentally thereby in behalf of many thousands of citizens of our own country who need their help.

A third obvious fact is the lack that still exists in the United States, among many people, of adequate medical attention both for diagnosis and for treatment. The costs of medical care have risen so high that many of our citizens cannot afford them. Some are insured, but many are not. In some way or other, which must be decided by care-

ful, conscientious and friendly discussion, such people must be protected and not left merely as a casual burden and charge for the medical profession or public purse, or both. The private practice of medicine should continue without interference, and the adequate care of the health of those unable themselves to pay for it should certainly necessitate neither the general socialization of medicine with its disadvantages as we see it elsewhere in the world today, nor the pauperization of our improvident people or of those unable financially to meet all the costs of medical care. This problem will take years still to solve. To my mind it is, however, less urgent than that of medical research, whose function it is eventually to make hospitals unnecessary.

Finally, we come to the most important of all the applications of *la médecine du coeur*—namely, the international. Fewer doctors are involved in this, but those that are realize its tremendous significance and power for good in these troubled times. It is a challenging but rewarding privilege to have a share in this work, which can be as potent a factor for peace as any in existence today. Without peace during the next generation all mankind will suffer, and attempts to advance in medical research, teaching and practice will be nullified. In fact if further and more devastating wars take place our civilization, including the present advanced state of medicine, can be set back a thousand years. With peace we can make great strides in the advancement of health for all the people of the world. Nothing else is so likely to maintain peace as the solicitous regard for the health and happiness of every inhabitant on this old planet of ours. We doctors are actually in a better position to accomplish this through the establishment of friendly and co-operative relations with the medical professions of other countries than are any other groups—in business, law, government or military circles. We have no ax to grind. We doctors are close to the hearts of all the world's citizens, and so by our own international medical friendships we surely can advance the peace of the world.

Medical congresses, visiting lecturers and medical traveling fellows can all play a role, but the most useful function of all, in my experience and in that of a good many others, as noted by neutral observers in many lands, has been played by the medical missions that have gone out to foreign lands, especially to those that have been ravaged by war, under the aegis of the Unitarian Service Committee. It is of these, as an example of what can be done, that I would like to speak briefly now, and for which I would ask your vigorous support.

Medical missionaries have traveled abroad for generations to do good, and they have done good, often but little known, but nevertheless of much significance in our international friendships, as in the case of my old acquaintance, Paul Harrison,

who has just completed thirty years of the ablest surgery and of setting a Christian example in Arabia Relief missions have gone to every corner of the globe to succour people in need at times of epidemic disease, famine or disaster. I myself was privileged to spend a few months in Northern Greece in 1919 to help in the control of exanthematic typhus, a serious disease, which, like malaria, has now been largely wiped out in that part of the world.

The special teaching missions of which I speak are, however, something new and more important than other missions in the past. They have gone out during three consecutive years to establish or renew medical associations between the medical profession of our own country and those of other lands, many of which had been crushed down by the iron heel of the invader with abolition or reduction to a minimum of medical education, research and practice. We went throughout the countries in central and southern Europe to share our good luck and to repay a little of the debt that the doctors of the new world owe to the old.

I myself was privileged to serve on two of these missions, the first to Czechoslovakia in 1946 and the one to Greece and Italy in 1948. Other missions of similar nature went to Poland in 1946 and again more effectively in 1948, to Austria in 1947, to Finland and to Germany in 1948, to Colombia in South America in the fall of 1948, and most recently to the Philippines. Still another smaller group went to teach at the medical school for displaced persons in Bavaria last summer. New missions will be needed for other parts of the world, — for example, India, — but we must not forget to follow up especially those already carried out.

Each of these teaching missions has been composed of a group of professors, numbering from 6 to 16, from several different medical schools in this country and even from Canada or from countries abroad, presenting in lectures, demonstrations, and conferences (with the help of interpreters and student guides) various special fields in medicine, surgery, the preclinical subjects (such as physiology) and dentistry. Thus each group has acted as a peripatetic medical school carrying good will and friendship as well as medical knowledge throughout these foreign lands. The invitations came to us from the foreign universities themselves, but the purpose and success of the missions quickly appealed to UNRRA, to WHO, to the peoples themselves, and to the governments of the countries involved, and resulted in warm support and the most cordial reception everywhere. An excellent press publicity followed the course of each mission as it traveled through the countryside.

The enduring effects of such missions are still seen in Czechoslovakia, where, despite the Communistic regime and the serious hardships suffered therefrom, our friends, medical and nonmedical, made by the mission in 1946, have continued to

be our friends as was clearly evident during my return visit there a year ago and by correspondence ever since. In the other countries too we have made and have held many friends. In these difficult days all this is bound to count in the long run. What we would have liked most of all to do would have been, and would still be, to re-establish a friendly medical contact with the USSR. We offered our services, but they were not accepted by the dictatorial group in power at the moment, I am sure that the doctors and the Russian people themselves would have welcomed us from their hearts and will do so one day. Meanwhile at the present time all indications seem to point to the political control of science in general and of medicine in particular in the USSR, resembling a good deal the Nazification of German medicine under Hitler, which not only blocked advances in medicine in Germany but actually resulted in a deterioration.

We hope that we may have the chance to share our medical experiences with our colleagues on the other side of the iron curtain when that curtain eventually is swept aside. This could be the beginning of a real friendship throughout the world. Meanwhile we should, with everlasting patience, constantly demonstrate to all parts of the world with which we can get in touch by personal contact, or by writing or radio, including the peoples immediately adjacent to the USSR as well as whatever inhabitants or citizens of the USSR we can reach, that we desire not to impose, but simply to share with all the world our way of life. It is very clear to those of us who have been privileged to make adequate comparisons that this way of life of ours, imperfect as it yet is, has advanced to a higher level than any other, standing as it does for freedom and happiness of all humanity, a precious heritage that we must forever defend from ruthless aggression. I personally believe that we should do more than pay lip service to this idea. We should by our own example and effort become active crusaders. In this small world today we are our brothers' keepers.

Let me emphasize once more the fact that these particular medical missions of ours were not simply "cold-blooded scientific groups." We did, of course, dispense and exchange by word and deed much scientific knowledge, but we did much more than that. We were the bearers of *la médecine du cœur* from this fortunate land of ours to our less lucky colleagues overseas. I have spoken of this particular activity in medicine internationally because it is a good example of what can be done and because I am myself familiar with it. There are, of course, other ways for the medical profession to help out in world affairs.

And so, my friends and colleagues, members and future members of the Massachusetts Medical Society, what a privilege and challenge is ours in the practice of *la médecine du cœur* for our patients,

toward each other, to our communities, for the national public health, and last but not least in our international relationships for the peace and happiness of all mankind!

In closing, let me quote again from our friend Petit

Voula, mon cher Forlis, ce qu'il fallait te dire,
Pour guider, en ami, cette ardeur qui t'inspire
Loin de te détourner par d'effrayans tableaux,
J'ai même en les peignant retenu mes pinceaux,

Mais, sans t'épouvanter d'un récit trop fidèle,
Suis courageusement le penchant qui t'appelle
Au bonheur des humains consacre ton repos
Et que l'art de guérir compte aussi ses héros

And that, my dear Forlis, is what I had to tell thee,
In order to direct, as a friend, the ardor which inspires thee
Far from turning thee away by frightening tableaux,
I have, in painting them, restrained my brushes
But, without the distraction of too exact a recital,
Follow courageously the leaning that calls thee
To human happiness consecrate thy repose,
And let the healing art also count its heroes

TREATMENT AND PROPHYLAXIS OF PULMONARY EMBOLISM BY VEIN INTERRUPTION*

COMMANDER MARION LEE CONNERLEY (MC), U.S.N.,† AND
CAPTAIN JOHN H. L. HEINTZELMAN (MC), U.S.N.‡

CHELSEA, MASSACHUSETTS

FOR the years 1944 and 1945, an average of 1 to 3 patients died each month at the United States Naval Hospital, Chelsea, Massachusetts, as a result of pulmonary embolism. The diagnosis in 17 of these patients was substantiated by autopsy. It therefore became apparent that some form of treatment must be instituted in an attempt to reduce the toll claimed by this scourge of surgical procedure in New England. In an effort to obtain some useful data that might be a contribution to this problem in general, a regime consisting of interruption of femoral, iliac or inferior-vena-cava venous pathways was adopted. A consistent, single form of treatment seemed more logical, if one desired to obtain data, than the treatment of some patients with heparin, some patients with dicumarol and some by ligation, or a mixture of the three. This report analyzes thirty-six months' experience with these surgical approaches to the treatment and prophylaxis of pulmonary embolism from December, 1945, to November, 1948.

DEFINITION

Thrombophlebitis (phlebothrombosis) is a pathologic process characterized by the occlusion of venous channels, partial or complete, static or progressive, by blood clot, portions of which are liable to fracture and dissemination through venous pathways to the lungs producing infarction of variable degree.

ETIOLOGY

Thrombophlebitis and phlebothrombosis are treated jointly in this discussion, since we now believe both procedures give rise to pulmonary em-

bolism, should a patient succumb to a pulmonary embolism, it matters little whether his original blood clot was bland or inflammatory. It does make a difference in diagnosis, the bland type being much more difficult to detect.

Etiologically no explanation can be given as valid, there are perhaps four groups of conditions that are thought to be contributory:

Venous Pressure

In some diseases there is a definite lowering of venous blood pressure. In some positions there is a lowering of venous blood pressure. With less "urge" to maintain the velocity of venous blood through its channels, there may be some inducement to blood clotting, organization and thrombosis.

Infection

The inflammatory picture and the consequent syndrome of thrombophlebitis are too well known to require elaboration. It should be said, however, that infection, likewise, may give rise to thrombosis.

Mechanical Stagnation

If some of the impetus for blood to return to the right side of the heart is due to muscular activity, alternate contraction and relaxation and so-called "milking," aided by the action of vein valves, anything that may act to counter this influence may considerably affect thrombosis of the vessel. Intra-abdominal disease, cardiac decompensation, prolonged bed rest and so forth may contribute.

Abnormality of Prothrombin Metabolism

This process is little understood actually, and it is only suggested here that a constitutional

*The opinions or assertions contained herein are the private ones of the authors and are not to be construed as official and reflecting the views of the Navy Department or the naval service at large.

†Chief of surgery, United States Naval Hospital.

‡Chief of medicine, United States Naval Hospital.

factor may predispose to ante-mortem, intraluminal venous thrombosis under certain circumstances

SYMPTOMS

Symptoms are really few and given so little credence by the patient, and often by the doctor, that they are frequently overlooked. Except for the diagnostic symptomatology of pulmonary embolism familiar to all, there are actually only two pre-embolic symptoms: minimal cramps in the calf of the leg, and, if the patient is ambulatory, a slight lump.

That even these minimal pains may not be overlooked, patients are questioned daily on the presence of pain in the calf and pain upon walking. Often the patient remarks that there is some tenderness in the back of his leg upon moving his foot, but he is sure it is due either to the weather or to muscular rheumatism, which he has had before.

PHYSICAL SIGNS

Physical signs, fortunately, are more numerous. Early in our experience we reviewed our patients and our theories with Dr. John Homans, the pioneer in this particular field. He was of the opinion that most of the physical signs we stressed occurred in the relatively late stages of thrombophlebitis and rarely, if ever, in phlebothrombosis. However, owing either to the age group of patients with which we deal or to the fact that patients are carefully and routinely examined with definite signs in mind, we have yet to see a patient with pulmonary embolism who did not exhibit one or more of the following physical signs before the incident. Each patient in bed must be inspected carefully for the presence of these signs each day, often the slight calf-compression discomfort is fleeting, and in the next day the patient may be the victim of embolism.

Changes of Skin Temperature

These can be determined readily if the examiner places the palm of his hand upon the surface of the leg being examined. Often, the skin of the affected leg is cooler to the touch than that of the unaffected side. Gross temperature changes detected in this manner are usually accompanied by cyanosis or skin blanching, sometimes a definite sense of clamminess is discerned. More frequently, however, some objective form of skin-temperature determination must be made. We use the comparatively simple method of determining skin temperature with the McKesson thermocouple operating on a Wheatstone-bridge principle. These readings do not need to be corrected for room temperature and humidity, for all we seek is the relative temperatures of the two legs.

If the underlying process is inflammatory the temperatures will be elevated on the affected

side over that of the opposite side. This, of course, may be attended by redness and other signs of inflammatory reaction.

We believe the common finding is decreased temperatures and think that it is caused by a concomitant spasm of the arterioles stimulated by the presence of a blood clot in the deep venous system. The close physical relation of the femoral vein and artery and the periphlebitis extending toward the arterial adventitia would provide adequate stimuli for such a sympathetic response.

Decreased Arterial Pulsations

Decrease in the strength of pulsation of the dorsalis pedis and posterior tibial arteries of the affected side is also a manifestation of an accompanying periarterial sympathetic stimulation.

Positive Homans's Sign

This should be more properly termed the dorsiflexion sign according to Dr. Homans, but it was he who called attention to its significance and we regard it as specific for thrombophlebitis and phlebothrombosis. Acute dorsiflexion of the foot will produce pain not only in the calf muscles of the affected side but also, in some cases, over the femoral canal. This is probably due to the tension placed on the diseased vein.

Calf Pain on Compression

Gentle to moderate compression of the calf of the affected leg is frequently most disturbing to the patient should a blood clot be present in the femoral system.

Swelling of the Affected Leg

Whether owing to associated lymph stasis, venous stasis or periarterial sympathetic action, the affected leg is increased in diameter when compared to the unaffected leg. The superior extent of the increase in diameter usually lags behind the level of the thrombus. When the calf is enlarged, we believe that the thrombus is at least in the common femoral vein and, when the thigh is enlarged, in the iliac vein. The diameter of each leg should be measured at exactly the same level, and our routine practice is to strike a level midway between the anterior superior iliac spine and the medial condyle of the femur in measuring the diameter of the thigh. The diameter of the calf is measured at a point midway between the level determined as above and the medial malleolus of the tibia.

Tenderness over the Course of the Vein

A vein harboring a comparatively active thrombotic process usually gives rise to some tenderness on pressure. Here again tenderness over the popliteal vein suggests thrombosis extending into the femoral vein, and, by the same token,

tenderness over the femoral vein at the groin suggests involvement of the iliac vein. In a relatively thin, co-operative patient one can occasionally elicit tenderness upon pressure over the iliac vein. This indicates involvement at least as high as the lower portion of the inferior vena cava. It must be remembered that the drastic palpation required to reach the region of the iliac vein will produce tenderness in a normal person, therefore, it is the comparative tenderness that becomes important.

Temperature, Pulse, Respiration and Blood-Pressure Elevation

Thrombophlebitis and phlebothrombosis, particularly as the process advances, will give rise to a slow, gradual elevation of temperature, pulse, respiration and blood pressure. Even in a patient who is doing well postoperatively, and in whom there is elevation in any or all of these factors, thrombophlebitis should be suspected, unless some other adequate etiologic agent can be definitely established for his reaction.

TREATMENT

Immediately upon the discovery of the presence of any one or more of the symptoms and signs of thrombophlebitis pointed out above, the chiefs of medicine and surgery are notified. These medical officers go over the patient again, and upon confirmation of the diagnosis, the patient is sent to the operating room without further ado.

The finite location of vein division depends upon the level at which the thrombus is assumed to be. If the thrombus is assumed to be in the popliteal vein or lower, bilateral common-femoral-vein interruption is performed. If the thrombus is assumed to be present in the common femoral vein on the right side, right-common-iliac and left-common-femoral interruptions follow. If the thrombus is assumed to be in the left femoral vein, owing to the technical difficulty of ligation of the left common iliac vein, an inferior-vena-cava ligation and division is performed.

After operation the patient is returned to the ward with his legs moderately elevated, usually only by means of the elevator of a Simmons bed, and with the pain controlled by sedation as necessary.

All patients whose femoral, iliac or inferior-vena-cava pathways are interrupted show some degree of swelling of the extremity after operation. To diminish the swelling and to prevent it from becoming chronic the following regime is used.

Before arising from his bed the patient is instructed to lie on his back and perform "bicycle" exercises for ten minutes.

With the legs still elevated, elastic bandages

are applied, including the foot, from the ankle to the groin in figure-of-eight fashion.

The patient then gets out of bed and leans over the side of the bed in such a way that his hips are at the edge of the mattress and the body weight is supported by the abdomen, chest and arms.

In this position the patient "walks" for ten minutes without bearing weight.

The patient may then be ambulatory.

After whatever exercise or ambulation the patient elects, he returns to bed, elevates his legs and removes the elastic bandages.

This regime is maintained for two weeks every time the patient arises from bed.

Usually, no swelling is noted upon ambulation after this two-week period of graded exercise. Should any swelling develop, however, the entire procedure is repeated for a second session of two weeks.

SEQUELAE

During the period 1945 to 1948, vein interruptions have been performed in 67 cases. Of these, 51 were bilateral femoral-vein divisions, 6 were a combination of right-common-iliac and left-common-femoral divisions, and 10 were divisions of the inferior vena cava.

In all these patients some amount, either minimal or maximal, of lower-extremity swelling occurred postoperatively. The swelling was most severe after interruption of the common femoral vein. It was moderate after right-common-iliac and left-femoral procedures, and it was minimal after vena-cava operations. The edema was transitory, never over four weeks' duration, except in 2 patients, both of whom had superficial femoral-vein interruptions. One of these patients, who was about sixty years of age, had had persistent swelling of both lower legs for well over eight months. This persistent edema was relieved by lumbar sympathetic novocain block, by 0.3 gm of etamon chloride solution intravenously administered. A bilateral lumbar sympathetic neurectomy was performed on this patient, with dramatic relief. It remains to be seen whether this is a permanent result. The other patient was an eighteen-year-old sailor who had an acute inflammatory thrombophlebitis following a basketball injury. After six months of unrelieved lower-extremity swelling following a superficial femoral-vein division, a bilateral lumbar sympathetic neurectomy was done. Complete remission of all swelling and disability resulted.

In our experience, which is limited not only in numbers but also in age group and which is further restricted by therapeutic ligation rather than prophylactic ligation, so far as the thrombophlebitic process is concerned, we have not seen the persistent chronic edema described by other clinics after

common-femoral-vein interruption above the saphenofemoral junction or after common-iliac and vena-cava interruptions

The second sequela, which we have noted in all patients, was the cyclic recurrence of an acute thrombophlebitis picture in the portion of the venous system peripheral to the level of venous interruption. This was often severe enough to require considerable morphine and, again as suggested by Dr Homans, it is to be expected in ligated veins that contain thrombi. These cycles of thrombophlebitis were usually limited to two or three episodes of three to five days each. In all cases they completely disappeared after three weeks.

In a patient whose collateral venous circulation is not yet completely established as a result of intravenous disease, a rather alarming amount of cyanosis of the extremity involved will be noted immediately after operation. However, just as the collateral venous pathways are established in thrombophlebitis, so are they established after interruption. In the course of twenty-four to forty-eight hours, the cyanosis will disappear, and the leg regain its normal preoperative color. We have noted this phenomenon in 2 patients: an elderly man with cardiac decompensation, who complained of severe cramping in his legs and constricting sensations of his chest, and a forty-year-old man, whose femoral veins were divided after celiotomy at which inoperable Hodgkin's disease of the adrenal glands, mesenteric lymph nodes and jejunum was found. In both cases at the end of forty-eight hours a discoloration was not apparent. Fractional spinal anesthesia of procaine solution to destroy only autonomic nervous activity is used as immediate treatment when this phenomenon occurs.

RESULTS

Among these 67 cases 2 patients died.

The first was a twenty-one-year-old Marine who had had three previous pulmonary emboli following avulsion of his left arm by an airplane propeller. He had received two courses of heparin and one course of dicumarol. On the day the regime described above was instituted, he had a fourth pulmonary embolus. The inferior vena cava was operated on, and a solid thrombus was found extending above the right renal vein and so organized that it could not be detached from the vein wall. This patient died on the operating table. Autopsy revealed a solid thrombus completely occluding the left renal vein, extending up into the right side of the heart and, in addition, propagating into the superior vena cava.

The second patient was a fifty-year-old lieutenant colonel in the Marine Corps, on whom an orthopedic procedure had been performed ten days previously. He was seen immediately after a pulmonary embolism. In obvious distress, he was taken to the operating room immediately, and the right common

iliac and left common femoral veins were interrupted. He did well after operation and was returned to the ward about 8 o'clock in the evening. Between that time and 6 o'clock the next morning he received four whole-blood transfusions of 500 cc each, two plasma transfusions of 500 cc each and two liters of physiologic saline solution intravenously. Although permission for autopsy was refused, it seemed apparent to all concerned that this man had died in severe pulmonary edema that was due to the uncontrolled administration of a large amount of fluid.

These cases must be considered as operative deaths and accredited to vein interruption. It is not believed that they, in any way, disprove the efficacy of this form of treatment and prophylaxis of pulmonary embolism.

Since January, 1946, there has been only 1 death from pulmonary embolism in the United States Naval Hospital, Chelsea, Massachusetts. This occurred in a sixty-five-year-old retired captain in the Navy, in whom the diagnosis of thrombophlebitis was made, but operation not performed.

The previous mortality in cases of pulmonary embolism was 0.5 per cent of all admissions. The average age was forty-one and six-tenths years, with a range of seventeen to eighty-four years. The vein-interruption rate, at present, is 0.5 per cent of all admissions. The average age is thirty-nine and two-tenths years, and the range eighteen to ninety-two years of age.

The coincidence is striking.

TECHNIC

A considerable amount of literature is available describing the various methods of performing vein interruption. Briefly, the femoral-vein interruptions are performed under local anesthesia through a longitudinal incision above the level of the saphenofemoral junction. At least 2.5 cm of vein is removed to prevent recanalization. The dictates of the Halsted school of surgery are followed rigidly, interrupted sutures and ligatures of No. 00 cotton being used.

The right common iliac vein is divided preferably under spinal anesthesia, but occasionally under pentothal and curare, or cyclopropane and curare, inhalation anesthesia. A right pararectus incision is used and carried down through the anterior rectus sheath. Sliding laterally to the right rectus muscle an extraperitoneal approach is made to expose the right common iliac vein. Should clot be encountered in the common iliac vein, conversion to the following operative field is quite feasible when this approach is used.

The inferior vena cava is approached through a similar type of skin incision, after which the right rectus muscle is retracted laterally and the peritoneum entered. The cecum is drawn laterally

and superiorly to the right, and an incision made into the posterior peritoneum medial to the right ureter. This incision is carried as high as necessary to demonstrate the right renal vein. A transperitoneal approach is used to the inferior vena cava, because we believe that such an exposure allows considerably more control of the situation should an untoward event occur. Any of the extraperitoneal approaches to this vital structure give adequate exposure for division, but little control should the distal stump of inferior vena cava slip away.

We do not believe in retrograde aspiration of a blood clot from a vein owing to the risk involved in removal of the clot intact. If the preoperative diagnosis of thrombus level is in error and an intraluminal blood clot in the common femoral vein demonstrated, the wound should be closed without disturbance of the vein, and an immediate attack made on the common iliac vein. Owing to the negative pressure in the inferior vena cava established by the heart beat and diaphragmatic action in respiration, we believe that placing the patient in Fowler's position actually affords little protection against the liability of an embolism.

SUMMARY AND CONCLUSIONS

Thrombophlebitis and phlebothrombosis can be treated by interruption of the common femoral vein, common iliac vein or inferior vena cava to provide prophylaxis against pulmonary embolism.

If careful, daily examination of patients after operation and those with cardiac disease is performed, signs and symptoms of thrombophlebitis and phlebothrombosis usually present themselves prior to pulmonary embolism.

Recurrent thrombophlebitis appears postoperatively but can be reduced to a minimum by graded exercises without postphlebotic syndromes in most patients.

The postphlebotic swelling syndrome may be effectively treated by bilateral lumbar sympathetic neurectomy, if further observations confirm the results of the 2 patients discussed above. These were the only patients in whom edema lasted over four weeks from the date of interruption.

Protection of the patient from pulmonary embolism by surgical interruption of selected veins can be accomplished with an insignificant mortality without the danger of massive delayed hemorrhage and the numerous critical laboratory observations required when anticoagulants are administered.

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SPLENIC-VEIN THROMBOSIS FOLLOWING TRANSTHORACIC GASTRECTOMY AND INCIDENTAL SPLENECTOMY*

STUART QUAN, M.D.,† AND BENJAMIN CASTLEMAN, M.D.‡

BOSTON

ALTHOUGH thrombosis of the splenic vein is infrequently reported in the literature,^{1, 2} it is common knowledge among surgeons that this condition may follow splenectomy. In fact, local thrombosis at the site of ligation of the splenic artery and vein with extension back to the first branching vessel is to be expected. This degree of involvement of the splenic vein, however, should be symptomless, but it is potentially important because of possible extension into the portal venous system and as a source of emboli to the liver. Since splenectomy is usually performed for definite diseases of the spleen such as trauma, focal parasitic infection and tumors, or for diseases of the hematopoietic system favorably influenced by splenectomy such as hemolytic jaundice, thrombocytopenic purpura and Banti's syndrome, the risk of extensive splenic-vein thrombosis postoperatively has to be taken. With the introduction of the transthoracic approach to gastric surgery and the associated incidental splenectomy, the possibility of postoperative splenic-vein thrombosis assumes more importance.

Up to 1946 such normal spleens were removed in 70 cases at the Massachusetts General Hospital

TABLE 1 Lesions Resected with Which Incidental Splenectomies Were Performed*

LESION	NO OF CASES
Carcinoma of stomach (8 transabdominally)	48
Carcinoma of esophagus	11
Miscellaneous gastric lesions (3 transabdominally)	4
Miscellaneous abdominal lesions (transabdominally)	7
Total	70

*Unless otherwise stated operations were through the transthoracic approach.

The majority of these spleens were removed incidental to transthoracic resections of a carcinoma close to the cardia, in either the upper stomach or the lower esophagus (Table 1).

The reasons for removing the spleen are presented in Table 2. Facilitating the operation by providing more adequate exposure for complete removal of the tumor was by far the most frequent reason. On other occasions the surgeon believed that it would be wise to remove the spleen so that it would not drag on the site of bowel anastomosis. The opera-

tor's note in 12 cases contained no specific statement why the spleen was also removed, but one may assume that it was also to facilitate the operation. Involvement of the spleen or pancreas by tumor represented another frequent cause for splenectomy. Thus, in 19 cases the tumor either was adherent to the capsule of the spleen or had actually invaded the splenic pedicle or hilus. An additional 6 cases

TABLE 2 Reasons for Splenectomy

REASON	NO OF CASES
To facilitate operation	20
Not stated but probably to facilitate operation	12
Operative trauma	13
Tumor adherent to spleen, splenic pedicle or splenic artery	19
Tumor adherent to or involving pancreas	6
Total	70

showed tumor involvement of the tail of the pancreas as well as the spleen. Surgically induced trauma to the spleen, such as inadvertent injury to the organ's blood supply or persistent capsular oozing after prolonged retraction of the organ, accounted for 12 splenectomies.

Eighteen patients died within forty-five days of operation, and all but 1 were submitted to post-mortem examination. As was to be expected, most of these cases showed local thrombosis of the splenic vein for short distances from the site of ligation. There were 5 cases, however, that showed thrombosis of the splenic vein and more extensive involvement of the portal system. Table 3 describes the extent of the thrombosis and the sequelae in each case. In 4 of these cases the thrombosis had extended into the portal vein and its intrahepatic branches to produce infarcts of the liver. Jaundice was present in Cases 1 and 3.

Case 1§ represents the only case in which the development and progression of the postoperative splenic-vein thrombosis turned out to be the main cause of death, and it was this case that stimulated the present study. It is presented in detail.

A forty-two-year-old wardman was operated on for the removal of an extensive scirrhous carcinoma of the stomach. In an attempt to remove all the disease, a total gastrectomy, transverse colectomy, splenectomy, esophagojejunostomy, jejunojunostomy and complementary cecostomy were performed. The immediate postoperative course was uneventful except for a three-day spike of temperature to 102° F, and he was discharged on the 20th postoperative day. He did well for 1 week on a six-meal bland diet, with only occasional transient abdominal pains, but then, 26 days after

*From the Department of Pathology and Bacteriology, Massachusetts General Hospital.

†Formerly intern in pathology, Massachusetts General Hospital.

‡Assistant professor of pathology, Harvard Medical School, pathologist, Massachusetts General Hospital.

§This case has already been published.¹

and superiorly to the right, and an incision made into the posterior peritoneum medial to the right ureter. This incision is carried as high as necessary to demonstrate the right renal vein. A transperitoneal approach is used to the inferior vena cava, because we believe that such an exposure allows considerably more control of the situation should an untoward event occur. Any of the extraperitoneal approaches to this vital structure give adequate exposure for division, but little control should the distal stump of inferior vena cava slip away.

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produce marked congestion, atrophy and necrosis of the central parts of the lobule — a lesion that is often called “incomplete infarction” or “atrophic red infarct”^{6,7} (Fig 1). When an interlobar branch of the portal vein is occluded, however, the systemic collateral circulation is usually insufficient to prevent a true infarct. Multiple incomplete infarcts were found in Cases 2, 3 and 5. That these infarcts are not necessarily produced by extension of the thrombus into the intrahepatic portal-vein radicles, but by emboli from the splenic-vein thrombosis was demonstrated in Case 5, in which there was no thrombus in the main portal vein.

Mention must be made of the 52 patients who survived and of the 1 who died postoperatively but was not examined at autopsy. Careful review of their postoperative course revealed little or no clinical evidence that a splenic-vein thrombosis was present. Twenty-six of these patients had temperatures of 100 to 104°F up to fourteen days postoperatively. These elevations of temperature were not accompanied or explained by any clinical development, and after such an extensive operation, it would be foolhardy to attribute them to a splenic-vein thrombosis. In only 1 patient were there complaints of unexplained left-upper-quadrant pain, slight jaundice and a temperature of 102°F, all of which occurred on the fourth postoperative day and lasted several days. This clinical triad is probably attributable to splenic-vein or portal-vein thrombosis.

SUMMARY AND CONCLUSIONS

Seventy cases of splenectomies performed incidental to some other operation (predominantly transthoracic gastrectomies and esophagectomies for carcinoma) are reviewed.

Five of the 17 patients studied at autopsy showed extensive thrombosis of the splenic and portal veins, and in 1 with superior-mesenteric-vein thrombosis the death was directly attributable to the initial splenic-vein thrombosis. The others showed multiple incomplete infarcts of the liver, which, had death not occurred because of peritonitis or massive pulmonary embolism, might have produced symptoms of liver failure.

Of 52 patients who did not die postoperatively, only 1 had suggestive clinical evidence of an underlying splenic-vein thrombosis.

Although it is recognized that incidental splenectomy is often necessary in the course of gastrectomy and esophagectomy, the surgeon should be aware of

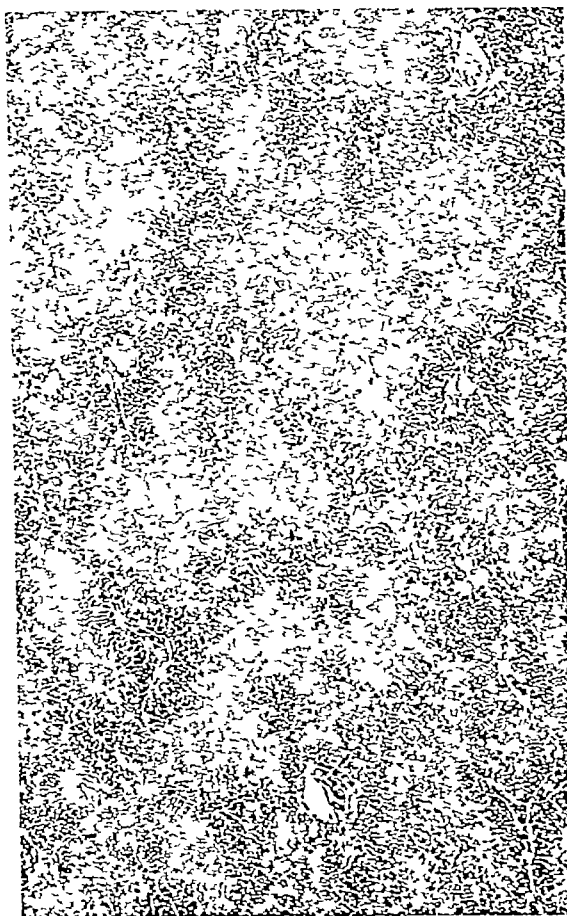


FIGURE 1 Photomicrograph, Showing Marked Central Necrosis of the Liver Lobules in an Area of Incomplete Infarction

the occasional complication of thrombosis of the splenic and portal veins and hepatic infarction.

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the operation, he began to complain of increasingly severe lower abdominal pain, which spread to the upper abdomen and down the left side. Pain became almost unbearable after a light supper. He had not vomited and had felt only slightly nauseated. His bowels had moved daily, although on the day of and on the day previous to this admission his stools had been hard and small in amount. Physical examination revealed a slightly distended abdomen, with generalized voluntary spasm throughout, maximal in the left upper quadrant. No masses were made out. Peristalsis was active and normal in pitch when first heard. Two hours later it was diminished to absent. A small amount of feces in the rectal ampulla was found to be guaiac negative. An x-ray film of the abdomen showed only an air-filled loop of small bowel in the left upper quadrant that was somewhat dilated and had a fluid level on standing. The white-cell count was 12,500. A Miller-Abbott tube was passed. Exploratory laparotomy under spinal anesthesia showed a moderate amount of dusky fluid and many white carcinomatous nodules in the small-bowel mesentery. There were no dilated loops of bowel, no evidence of obstruction and no leakage around the anastomoses. Postoperatively the temperature ranged between

Microscopical examination of the portal and splenic veins demonstrated definite organization of the thrombi, whereas those in the mesenteric vein and its tributaries were quite recent. The liver showed central congestion, but no definite foci of infarction were seen. There was also a pulmonary infarct.

DISCUSSION

Although only 1 patient (Case 1) had specific clinical signs and symptoms attributable to the thrombosis of the splenic and portal veins, which eventually spread to major branches of the superior mesenteric vein to cause gangrene of the small bowel and death, there were pathologic changes in the other cases that may have been contributing factors to the major postoperative complications—peritonitis and pulmonary embolism—to which these patients succumbed. For example, it is pos-

TABLE 3 *Complications of Splenic-Vein Thrombosis*

CASE No	HOSPITAL No	PATIENT	AGE	SEX	ANATOMIC DIAGNOSIS OF SURGICAL SPECIMEN	DAY OF DEATH POST OPERATIVE	EXTENT OF THROMBOSIS	MAJOR CAUSE OF DEATH
1	A-11149	V R	37 42	M	Scirrhus carcinoma of stomach with metastases to regional lymph nodes	33	Splenic portal and superior mesenteric veins	Thrombosis of splenic, portal and superior mesenteric veins gangrene of small bowel
2	A-11610	M K.	54	F	Epidermoid carcinoma of esophagus	17	Splenic vein completely occluded portal vein incompletely occluded multiple incomplete infarcts of liver measuring up to 15 x 18 cm	Pulmonary embolism, multiple
3	A-10203	G W	46	M	Adenocarcinoma of stomach recurrent in wall of lower esophagus	9	Splenic vein completely occluded portal vein and intrahepatic branches plugged with multiple thrombi multiple incomplete infarcts of liver measuring up to 8 x 8 x 5 cm.	Peritonitis acute left upper quadrant empyema bilateral
4	A-11197	E V R.	71	F	Scirrhus carcinoma of stomach	42	Splenic vein and artery entirely thrombosed portal vein and intrahepatic branches contained numerous small reddish gray firm thrombi	Massive pulmonary embolism empyema left peritonitis acute generalized
5	A-11702	W S	67	M	Carcinoma of stomach with metastases to lymph nodes and pancreas	7	Splenic vein for distance of 3 cm infarct of liver	Peritonitis acute pancreatitis pulmonary embolism and infarct uremia

99.6 and 100.5°F. The abdominal distention increased. There was no audible peristalsis. The patient complained of pain in the testes and penis. There was considerable vomiting and occasional hiccoughs. On the 3rd postoperative day jaundice developed. On the evening of the 5th postoperative day he suddenly went into shock, with profuse sweating and dyspnea. The blood pressure was unobtainable. The abdomen was quite distended, and peristalsis could not be heard. He died 10 hours later.

At post-mortem examination the peritoneal cavity contained about 1500 cc. of turbid, straw-colored fluid. Many pale-white carcinomatous seedings were present over the peritoneum and mesentery. Scars of the operative procedure described above were found, and their various lines of anastomoses were intact. Beginning at a point 100 cm from the origin of the jejunum and extending for about 100 cm, the small intestine was dark red, purple, fibrin coated, markedly edematous and gangrenous. In the mesentery all the veins to this loop were filled with ante-mortem, dark reddish, gelatinous thrombi, which extended into the superior mesenteric vein. The entire portal vein, its ramifications in the liver and the entire splenic vein were filled with reddish-brown, firm, adherent thrombi much older than those seen in the superior mesenteric vein and its tributaries.

sible that if the patients with multiple hepatic infarcts had not succumbed to postoperative complications, symptoms referable to the liver might have developed.

It is generally agreed that true infarction of the liver—that is, actual necrosis—occurs primarily as a result of occlusion of the hepatic artery or its branches. For example, accidental ligation of an anomalous hepatic artery in the course of surgery in the gall-bladder region produces total infarction, whereas emboli to the intrahepatic arteries in subacute bacterial endocarditis or secondary thrombosis of the intrahepatic arteries involved with arteritis nodosa are causes of multiple small infarcts.^{4,5}

Occlusion of the portal vein and its main branches does not result in a true hepatic infarct. It may

liveries, and abortions are considered separately. Comparable figures are given in Table 3.

From 1928 to 1937 there were 271 abortions, with 3 deaths — a death rate of 1.1 per cent. Two were due to sepsis, and 1 to ruptured aorta. From 1938 to 1947 there were 315 cases of abortion, with no deaths. These are not included in the above figures on maternal mortality.

The following are brief reports of the fatal cases during the last ten years.

CASE 1 Labor was induced in a 38-year-old para II. She was 12 days overdue and had had a superficial phlebitis. Labor was very rapid and severe. She had an easy, normal delivery. The baby was stillborn. Immediately after delivery the maternal pulse became very rapid, and soon imperceptible. Respirations were very rapid. The maternal heart could not be heard. Oxygen, caffeine, coramine and epinephrine were given, to no avail, and respiration soon ceased. Permission for autopsy was refused. The presumptive diagnosis was pulmonary embolism. When Steiner and Lushbaugh⁵ reported on amniotic embolism,

CASE 4 A 37-year-old para III, 8 months pregnant, was admitted to the hospital with abdominal pain and bleeding. There was marked edema. The blood pressure was 150/100. The patient had a mild convulsion and became comatose, her color was ashy purple, and the respirations were stertorous. The uterus was boardlike. A stillborn baby delivered spontaneously. Rather profuse bleeding followed. Intravenous administration of 25 per cent glucose and plasma was started, but the patient died. The diagnosis was premature separation of the placenta and eclampsia, confirmed by autopsy. It seems that the only chance to save this patient had been lost before she entered the hospital.

CASE 5 A 41-year-old primipara entered the hospital in mild labor with a blood pressure of 150/90. Two days before, the blood pressure had been 130/90. There was no albumin in the urine. Delivinal, 0.28 gm., and 100 mg. of demerol were given at 5:30 p.m. Labor progressed normally. At 8:00 p.m. the patient complained of headache, at 8:30 she became semicomatose and died in less than 1 hour. Autopsy showed eclampsia to be the cause of death. There does not seem to have been any chance to prevent this death.

CASE 6 This patient was a 39-year-old para III who had a rapid, severe labor. Shortly before delivery she had a

TABLE 4 Causes of Death in the Two Periods

PERIOD	CEREBRAL EMBOLISM	PULMONARY EMBOLISM	PLACENTA PREVIA	ECLAMPSIA	HEART DISEASE AND BRONCHOPNEUMONIA	POST-OPERATIVE SEPSIS	MESENTERIC THROMBOSIS	RUPTURED UTERUS WITH SEPSIS	EMBOLISM WITH AMNIOTIC FLUID
	NO. OF CASES	NO. OF CASES	NO. OF CASES	NO. OF CASES	NO. OF CASES	NO. OF CASES	NO. OF CASES	NO. OF CASES	NO. OF CASES
1928-1937	1	2	1	2	1	1	1	—	—
1938-1947	—	—	—	3	—	—	—	1	2*

*1 proved, 1 presumptive.

the marked similarity with their proved cases led to the opinion that this death was really due to embolism with amniotic fluid. If labor had not been induced, or if it had been slowed down, this tragedy might have been avoided.

CASE 2 A 43-year-old para III was delivered of a 9 lb., 9 oz., baby by midforceps. After delivery the patient seemed in good condition. Over the course of several days vomiting and marked distention developed. Four days after delivery the temperature began to rise, and chest pain developed, and on the 5th day the patient died. Autopsy revealed a rupture of the lower uterine segment, peritonitis, bronchopneumonia and an embolus in the inferior vena cava. Diagnosis of the difficulty or recognition of the gravity of the patient's condition might have saved her life.

CASE 3 This 39-year-old para II, with essential hypertension, was 6½ months pregnant. She had had a severe toxemia with her first baby. She was being checked daily in an effort to attain viability. The blood pressure varied from 160/100 to 224/120. An occasional + test for albumin was found. At noon on May 30, the blood pressure was 210/120 and a voided specimen showed a + test for albumin. The fluid output was equal to the intake. There was no pain, headache, scotoma or edema. At midnight she told her husband that she felt fine. Two hours later she had severe epigastric pain, vomiting and difficulty in breathing. The blood pressure was 290/140, and the pulse 60. Despite treatment, the patient became steadily worse and died. Autopsy showed a massive cerebral hemorrhage and the typical findings of eclampsia. It developed afterward that, unknown to the patient, both her mother and her mother's mother had died of convulsions in childbirth, and several aunts were known to have hypertension. This patient could have been saved if pregnancy had been interrupted early. It was a calculated risk in which it was believed that there would be time to intervene if the patient was watched carefully. The development of eclampsia was too sudden to permit this. More attention should have been paid to the minor warnings, and knowledge of the family history would have helped.

mild convulsion. The respiration became stertorous. After delivery the pulse was unobtainable, and respiration was labored and noisy. Oxygen was given constantly. Intravenous injections of glucose and plasma were given without benefit. The respirations gradually ceased, and the patient died. Autopsy revealed that death was due to embolism with amniotic fluid. Perhaps slowing of the labor would have prevented this death. This is another proved case of amniotic embolism added to the 12 reported by Watkins.⁶

It is perhaps not significant, but all these deaths occurred in older patients. A comparison of the causes of death for the two ten-year periods is presented in Table 4.

Eclampsia seems to be the major bugbear. In most cases the difficulty has been a failure to recognize and treat the disease in time. This is, in some cases, the fault of the physician, whereas in several the patient has been guilty of at least contributory negligence by failing to keep appointments or to seek medical advice until too late. It is not believed that any doctor has been negligent or culpable in the above cases. The results are good but can be better, and criticism is directed entirely to that end.

Morbidity rates have been figured yearly since 1939 in accordance with the standards of the American Committee for Maternal Welfare. The rate dropped from 7 per cent in 1939 to 4.6 per cent in 1940 and 3.4 per cent in 1941, and since then it has averaged about 2 per cent. Sulfonamides and penicillin must be awarded the credit for this reduction,

OBSTETRICS IN THE WINCHESTER HOSPITAL (1928-1947)

SANFORD H. MOSES, M.D.*

WINCHESTER, MASSACHUSETTS

IN 1938, a report on maternal mortality in the Winchester Hospital for the years 1928-1937 was published,¹ with the intention of demonstrating that good obstetrics could be practiced in a small hospital. This report covers the twenty-year period 1928-1947 and includes fetal-mortality statistics for the last ten years. It is believed that the publication of statistics from this hospital and discussion of the problems and results will be of value to those who practice in similar institutions. Most of the available statistics come either from large maternity hospitals or from city, state or national areas. The figures presented below show the results obtained in a small general hospital, which is where the bulk of obstetrics is done. Comparison between similar hospitals should lead to general all-round improvement.

For the last ten years, a yearly analysis of the obstetric work has been made and presented to the

ing them home early that it has been possible to deliver so many patients. The members of the staff have given perfect co-operation. When the hospital is overcrowded, the patients most able to do so are sent home. So far, all those really needing hospitalization have been kept as long as was really necessary. Table 1 gives the number of deliveries per year and the percentage of deliveries accomplished by cesarean section.

The indications for cesarean section have been reviewed prior to operation by the chief of service.

TABLE 2 Maternal Mortality

YEAR	NO OF DELIVERIES	MORTALITY
		%
1928-1932	1 074	0.258
1933-1937	1 206	0.24
1938-1942	1 935	0.125
1943-1947	4 137	0.072

TABLE 1 Deliveries and Cesarean Sections, 1928-1947

YEAR	NO OF DELIVERIES	CEASUREAN SECTIONS
		%
1928	224	8.6
1929	212	8.5
1930	228	5.7
1931	212	5.2
1932	198	7.0
1933	216	6.4
1934	225	7.1
1935	256	4.3
1936	245	2.8
1937	262	3.4
1938	285	2.1
1939	315	2.5
1940	340	1.15
1941	412	3.88
1942	577	2.25
1943	686	1.89
1944	701	3.7
1945	706	2.26
1946	942	2.96
1947	1102	3.44

staff. For the last year, monthly section meetings have been held. Both these points have, I think, been helpful in improving the quality of the work.

The number of deliveries has increased to a spectacular degree. The hospital has had to utilize every bit of available space and to encroach to a limited degree upon adjacent rooms. By this means the number of obstetric beds has been increased from 19 to 31, the Department of Obstetrics has still been maintained as an independent, isolated unit in the hospital. The doctors' room has been converted into a 3-bed labor room, giving 5 labor-room beds. In spite of the additional beds, it is only by getting patients out of bed early and send-

The main indications have been repeat section, cephalopelvic disproportion, placenta previa, premature separation of the placenta, toxemia and fetal distress, with a scattering for obstructing tumors, abnormal presentations, previous pelvic repair operations and the like. This system has served to eliminate the cesarean section for convenience. No reasonable indication has been refused, and the plan has worked well. Since 1933 no deaths have followed cesarean section, and in that

TABLE 3 Mortality Rates in Three Other Hospitals

HOSPITAL	YEAR	MATERNAL MORTALITY
		%
Wenatchee ²	1944 1945 1946	0.2
Illinois ³	1945	0.179
Boston Lying in ⁴	{ 1946	{ 0.15
	{ 1947	{ 0.15

time 212 patients have been so delivered. However, it is still believed that cesarean section is much more dangerous to the mother than delivery from below.

The maternal mortality, as reckoned by five-year periods, is presented in Table 2.

In the previous report¹ (1928-1937) 3 deaths, which were due to miscarriage, were included. These have now been deleted. The maternal mortality is figured on the basis of the number of de-

*Vice-chairman of staff, Winchester Hospital.

smallest percentage of autopsies was in the premature babies. Undoubtedly, some of the cases classed as prematurity alone would have shown additional causes of death if autopsy had been done. Moreover, the number of cases is not sufficient to give much statistical validity. However, in view of the agreement with other series of fetal deaths, some comment is justified. The most striking thing is that prematurity occurring in 3 to 4 per cent of all cases was a cause in 56 per cent of all deaths and in 65 per cent of all neonatal deaths. In many cases the cause of the prematurity was unknown but in about 35 per cent the situation was due to maternal conditions, such as maternal toxemia, premature rupture of the membranes, placenta previa and premature separation of the placenta, which were all about equally culpable. Better care of premature babies and the exertion of every effort to prevent premature delivery should offer the best chance of reducing the total mortality. Perhaps stilbestrol will be valuable here. Birth injuries occurred much more frequently in the full-term group, though more injuries in premature babies might have been revealed by more autopsies. Prevention of very rapid deliveries and improved obstetric judgment and skill offer hope of reducing this group. Deaths from erythroblastosis and congenital malformations should occur less often in future, owing to recent advances in

knowledge. In general, however, hope of improvement lies not in any one group but in painstaking vigilance and constant alertness to the possibilities of saving one baby here and another there.

Evaluation of these results has been helpful, and it is hoped that publication of them will be interesting and helpful to others. Publication of similar studies from other hospitals, so that various methods and technics may be compared by their results in actual "grassroots" practice, should be very fruitful in raising the general level of obstetric care.

15 Dix Street

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MEDICAL PROGRESS

ABDOMINAL SURGERY

ARTHUR W. ALLEN, M.D.,* AND CLAUDE E. WELCH, M.D.†

BOSTON

A REVIEW of the literature for the past year resulted in the abstracting of over 200 articles on surgical conditions of the abdomen that were considered of value. Since space is limited, all references except those given below are omitted. It is obvious that our selection of the contributions regarded as most pertinent to progress will, in the minds of some, fall short of a complete survey. We have tried, however, to present a fair estimate of the past year's work on new and controversial subjects.

SURGERY IN THE AGED

Cutler¹ reports the results obtained in a group of 204 aged patients operated upon for acute lesions. These were all inmates of a charitable institution

maintained for the care of the indigent in a metropolitan district. The over-all mortality was 44 per cent. The chief cause of failure was postoperative pneumonia, which accounted for 34 per cent of the deaths. One is bound to wonder whether some of these fatal pulmonary complications were embolic in origin since the group includes thigh amputation, intestinal obstruction and acute infections of various abdominal organs, all of which are known to be followed by phlebothrombosis and pulmonary embolism in a high percentage of older patients. It must be borne in mind that institutions for the sole care of the indigent do not have the facilities for early diagnosis and adequate preoperative and postoperative care found in large general teaching hospitals.

A correlation to the above statement is afforded by an excellent presentation by C. Stuart Welch,² who gives the data on 609 operations performed on

*Consultant in surgery, Massachusetts General Hospital.
†Clinical associate in surgery, Harvard Medical School; associate surgeon, Massachusetts General Hospital; consulting surgeon, Massachusetts Eye and Ear Infirmary.

but it is considered a creditable showing. The principal causes of morbidity were retention of lochia, upper respiratory infection, urinary infection and mastitis.

Figures on fetal mortality are the other side of the picture and of equal importance in an evaluation

deaths. This includes, however, only the first ten days and excludes babies under 1000 gm. No figures are given for the number of deaths after ten days. If the babies weighing under 1000 gm are included, as they are in this series, the total mortality is 3.2 per cent, again equally divided be-

TABLE 5 Comparative Figures on Fetal Mortality

INSTITUTION	TOTAL BIRTHS	GROSS DEATH RATE	STILLBIRTH RATE	NON VIABLE STILLBIRTH RATE	VIABLE STILLBIRTH RATE	TOTAL NEONATAL MORTALITY	NEONATAL MORTALITY AMONG PRE-MATURE INFANTS	NEONATAL MORTALITY AMONG INFANTS WEIGHING OVER 5 LB	PER CENTAGE OF PRE-MATURE INFANTS THAT DIED	PER CENTAGE OF ALL INFANTS WEIGHING UNDER 5 LB	VIABLE STILLBIRTH RATE
Winchester Hospital											
1938-1942	1 948	35.4	18.0	3.0	15.0	17.4	12.3	5.1	3.8	3.4	—
1943-1947	4 170	32.6	15.3	4.8	10.5	17.26	9.83	7.43	25.1	3.8	—
1938-1947	6 118	33.5	16.2	4.25	11.93	17.3	10.6	6.7	28.2	3.7	—
Boston Lying in Hospital ⁴											
1938-1942	16 814	36.0	—	—	20.0	16.0	9.0	7.0	26.0	—	—
1943-1947	13 240	39.0	—	—	21.0	18.0	9.0	9.0	25.0	—	—
Wenatchee hospitals ⁵	—	32.8	—	—	11.2	21.6	11.0	10.0	—	—	—
Chicago Lying in Hospital ⁷											
1941-1946*	17 657	—	—	—	—	12.5	—	—	—	—	12.4
Illinois hospitals (1944) ⁸											
All hospitals	125 534	—	—	—	—	20.9	—	—	—	—	20.0
Larger hospitals†	19 854	—	—	—	—	15.8	—	—	—	—	19.0

*Does not include statistics on infants weighing less than 1000 gm.

†Hospitals reporting 500 to 999 births.

of the quality of obstetric performance. Only the figures for the last ten years are available. All deaths before discharge from the hospital are reported, though some infants lived many weeks. Any baby that lived even for a short time and all stillborn infants over twenty weeks of menstrual age or over 14 inches in length were considered viable. Any baby weighing under 5 pounds was considered premature. One or two babies each year have been sent to an infants' hospital for special treatment, and some have died there. Inasmuch as these deaths occurred outside this hospital, they have not been included in this report though actually they should be charged against the mortality figures. If these cases are included there is an increase of about 1 or 2 per thousand in the figures. Two of these babies who died elsewhere had diarrhea of the newborn. In 1946 there were 7 sporadic cases, with these 2 deaths. That no real epidemic occurred is, I think, a tribute to the efficacy of the nursing technic. Table 5 presents the fetal-mortality record for the two five-year periods, along with comparable statistics from other hospitals for the same periods.

Standards of viability and prematurity vary in different clinics. Various inclusions and exclusions make it difficult to obtain comparable figures. The figures given by Potter and Dieckmann⁷ for fetal mortality in the Chicago Lying-In Hospital (1941-1946) offer an interesting example of this difficulty. They report a total mortality of 2.5 per cent, with 1.25 per cent stillbirths and 1.24 per cent neonatal

deaths between stillbirths and neonatal deaths—1.6 and 1.59 per cent respectively. These figures are almost identical with those in the Winchester Hospital series.

The causes of fetal mortality have followed the usually reported pattern.^{9,11} The percentages of

TABLE 6 Causes of Fetal Death

CAUSE	PER CENTAGE OF ALL DEATHS	PER CENTAGE OF STILL BIRTHS	PER CENTAGE OF PRE-MATURE DEATHS	PER CENTAGE OF NEONATAL DEATHS
Prematurity alone	25.7	—	46.0	32.0
Prematurity in addition to other causes	56.0	45.0	—	65.0
Congenital malformations	16.3	20.8	10.0	12.0
Birth injuries	14.4	5.5	0.2	21.8
Erythroblastosis	3.7	2.8	1.0	4.6
Maternal causes	25.0	25.0	34.8	24.0
Placenta previa, premature separation of the placenta, toxemia, premature rupture of membranes	—	—	—	—
Pressure on umbilical cord	3.1	7.0	0	0

death from various causes have been calculated and are shown in Table 6. They illustrate the relative importance of various causes of death in various situations. They do not total 100 per cent because rare causes were not included.

These percentages are not to be taken too seriously. Autopsies were done in about 35 per cent of all fetal deaths and in 60 per cent of the neonatal deaths among full-term infants. The

thors stress the need of careful preservation of the splenic vein in this procedure since the venous channels are thus left intact as anastomotic vessels.

A more radical attempt to eliminate the hazard of varices in Banti's syndrome is reported by Phemister and Humphreys¹⁴. Total gastrectomy was done in a case in which there were subsequently two episodes of bleeding. Transthoracic resection of the lower esophagus and stomach was carried out in another patient. In the discussion of this paper, Wangenstein¹⁵ stressed the acid-peptic digestive factor in bleeding from esophageal varices. In dogs with a simultaneously produced portal hypertension, a 90 per cent resection of the stomach will not regularly prevent ulcer provoked by histamine in beeswax. Without portal hypertension a 75 per cent gastric resection with short-loop retrocolic anastomosis will prevent this type of ulcer. Wangenstein described 3 patients subjected to extensive gastric resection for esophageal varices in 1945, 2 of whom were alive and well two years later. Pemberton¹⁶ advised early splenectomy in Banti's disease to prevent esophageal varices. Blalock¹⁷ reported a successful outcome after splenorenal anastomosis.

THE PANCREAS

Waugh¹⁸ presents the data from the Mayo Clinic on pancreatectomy up to January 1, 1947. Of 49 patients in this group, 6 had total pancreatectomy with a lower mortality than that in those who had partial pancreatectomy, owing he believes, to the leakage of the closed pancreatic stump in some of the earlier cases. The over-all mortality was 26 per cent. Of 11 patients operated upon for benign lesions there was a fatal outcome in 45 per cent, owing to the technical difficulties associated with inflammation. Thirty-eight patients had carcinoma, 21 per cent of whom failed to survive the operation. One-stage procedures carried a slightly lower mortality than the two-stage operations. The survival rate following pancreatoduodenectomy for carcinoma of the pancreas was discouraging, and the author questions whether or not a cholecystoenterostomy in these patients would not produce an over-all better outcome when the operative mortality for the radical procedure was taken into consideration. The survival period for carcinoma of the ampulla of Vater was more encouraging, as pointed out by several other observers.

The technic of pancreatoduodenal resection has been described by Cattell¹⁹ and a further appraisal of the procedure made by him more recently²⁰. He believes that patients with long-standing jaundice have a better chance for survival by a two-stage procedure. Fifty-two pancreatoduodenal resections have been done at the Lahey Clinic since 1942, with 9 deaths (17.3 per cent). Five of these were for benign lesions. Cattell²¹ believes that one can tell whether or not the obstruction is due to cancer

by the simple expedient of finding a dilated pancreatic or common bile duct. In nonresectable cases he believes that worthwhile palliation can be obtained by anastomosis of the dilated pancreatic duct to the jejunum.

Bartlett²² has reviewed the experience with pancreatic carcinoma at the Massachusetts General Hospital from 1941 to 1947. Seventy-eight patients were seen, and 83 per cent were operated upon. Thirty-two per cent of the entire group had a radical resection. The operative mortality was lower with the two-stage procedures. At the time of his report one patient was living five years and another eight months after operation. The average duration of life of the remainder was seven months.

Owens²³ calls attention to the danger of peptic ulceration following pancreatoduodenectomy if the hookup is such that the acid secretions of the stomach enter the jejunum proximal to the bile and pancreatic juices. He reports 3 cases with this complication. It is generally understood and practiced now that the bile duct and pancreatic duct be implanted into the jejunum proximal to the stomach segment.

Thompson²⁴ has recorded a patient living and well seven years after pancreatoduodenectomy for carcinoma of the ampulla of Vater.

THE GALL BLADDER AND BILE DUCTS

Sainburg and Garlock²⁵ report 75 cases of carcinoma of the gall bladder from the Mt. Sinai Hospital (New York City) between 1933 and 1946. Sixty-five patients were operated upon, and 64 of these were dead within thirty-five months. One patient was alive over thirteen years after operation. Abdominal pain in 77 per cent, jaundice in 38 per cent and a palpable mass in 64 per cent were the predominant symptoms and signs. Seven patients had unsuspected carcinoma revealed after cholecystectomy. Stones were found in all but 1 patient. Graham²⁶ pointed out that stones were found in only 8 per cent of metastatic carcinomas of the gall bladder. These studies further confirm our opinion that stones are a causative factor in carcinoma of the gall bladder. Fortunately, the percentage of cancer in all cases of gall-bladder disease is low. Therefore, this argument should not be used too freely in advising cholecystectomy for quiescent gallstones, since there are much better reasons for so doing. It should, however, be kept in mind.

Strictures of the common bile duct still occur too frequently. They represent such a serious complication that at times we have believed that the patients were unfortunate in surviving their original operation. It behooves every surgeon to consider the possibility of an anomaly of the vascular and ductal region. There cannot be too much caution used in the accurate visualization of all structures during cholecystectomy.

542 patients in the Carney Hospital (Boston) In this group of patients of seventy years or older, there was a mortality of only 11 1/4 per cent The author states that 5 per cent of the population of Massachusetts are over seventy years of age It is pointed out that these persons tolerate abdominal surgery poorly, with a mortality of 22 1/2 per cent in his series Furthermore, in biliary-tract lesions over half the patients had complicated problems, such as common-duct stones, acute cholecystitis and cancer of the gall bladder

TALCUM-POWDER GRANULOMA

Thirty-seven cases of postoperative complications due to talcum-powder granuloma are reported by Eiseman, Seelig and Womack² from the Barnes Hospital (St Louis) The range was from simple wound abscesses to fecal fistula and intestinal obstruction The lesions are most frequently confused with tuberculosis The chronicity of the disease is stressed, and it is compared with pulmonary silicosis There is a full review of the literature on the subject and the methods used for making the diagnosis microscopically

Swingle⁴ cites a patient who was operated upon fifteen times for talcum-powder granuloma with, finally, a fatal outcome Repeated attacks of intestinal obstruction were the reason for the large number of operations He states that the highest number of operations in any case previously reported was five The diagnosis was established by microscopical examination

The importance of this lesion cannot be overstressed It is almost certain that many operations for postoperative adhesions with obstruction have been done without any thought that talcum-powder granuloma is the underlying pathologic process Safe and suitable glove powder can now be obtained It is expensive at present, but serious consideration should be given to its general use Surgeons still using talcum powder should be conscious of the danger Sparing use of this substance on the hands and within the gloves, which must be carefully washed after they are put on, should help in reducing this hazard

HERNIA

Gross⁵ has presented a new and simple method of treatment for large omphaloceles The skin is underrmined on either side and sutured over the large sac, which has been carefully left intact The child is left with the large mass, which gradually recedes into the abdominal cavity during the first ten months of life At this time it is easy to resect the collapsed sac and repair the abdominal wall in an anatomic manner Three cases are cited, in all of which the patients recovered

Harkins and Schug⁶ report the follow-up results on 131 hernias repaired by the McVay technic (conjoined tendon sutured to Cooper's ligament) Three

recurrences were found two or more years after operation The authors have used the method on 367 hernias and point out its value because it is applicable to all types of inguinal hernia The article is well illustrated

There are certain defects due either to repeated operations or to trauma that are not easy to repair even with fascia lata Koontz⁷ gives a preliminary report on the use of tantalum-wire mesh in the closure of such defects He made a further report before the Southern Surgical Association, White Sulphur Springs, West Virginia, December 7-9, 1948⁸ The material is well tolerated in the tissues and causes no foreign-body reaction Although it apparently can be used next to the intestine (without immediate harm) if there is no peritoneal structure available, it is believed that a peritoneal protection should be obtained when possible It is further stated that skin with attached subcutaneous tissue of considerable thickness is preferable to skin alone The mesh is held in place by fine tantalum-wire sutures

Throckmorton⁹ reports the use of tantalum-wire mesh in 16 patients He has observed no wound complications or other evidence that this material was not well tolerated by the host There have been no recurrences in a follow-up study of three to twenty-six months

PORTAL HYPERTENSION

Blakemore¹⁰ reviews the subject and reports 40 cases in which portacaval anastomosis was completed There were 5 postoperative deaths He divides the types of liver disease that may be benefited by this operation into five groups as follows schistosomiasis, Banti's syndrome, cirrhosis of the liver, ascites and posthepatitis cirrhosis The operation is indicated if there has been massive gastrointestinal hemorrhage from esophageal varices or if the varices can be demonstrated by x-ray examination

Linton, Hardy and Volwiler¹¹ divide the patients suitable for portacaval shunts into three groups intrahepatic portal-bed block due to portal cirrhosis or thrombosis of the hepatic veins, extrahepatic portal-bed block due to congenital or acquired obliteration of the portal vein, and a combination of the first two types Of 7 patients with the intrahepatic type operated upon, only 2 survived Deaths in this group were due to liver failure In 8 patients with extrahepatic block, all survived operation, and only 1 has bled since the procedure was done Linton prefers the splenorenal anastomosis with preservation of the kidney, through the thoracoabdominal approach

Welch¹² reports a successful suture technic with the aid of the Thomas-Smith intestinal clamp in an anastomosis between the portal vein and vena cava Everson and Cole¹³ have ligated the splenic artery in 3 poor-risk patients with portal hypertension The immediate results were satisfactory The au-

between 1939 and 1948. He stresses the importance of the transthoracic approach, the use of antibiotics, including both penicillin and streptomycin locally and parenterally, the use of oxygen post-operatively, continuous gastric suction during operation and drainage of the pleural cavity for forty-eight hours after operation. There were 16 patients who had nonfatal complications, and there was an over-all operative mortality of 11.6 per cent.

An improved method of cytologic examination of gastric secretions is presented by Ulfelder, Graham and Meigs⁴³. After careful lavage of the stomach the patient is left with an inlying gastric-suction tube overnight. The next morning washings are obtained and centrifuged. Smears are then studied by the Papanicolaou technic. Forty-five out of 48 patients studied had satisfactory smears. The 3 failures were in patients with almost complete obstruction. In 12 of 14 patients with cancer the diagnosis was correctly made by this method. One patient with lymphoma of the stomach showed no abnormal cells in the stomach secretions.

MacDonald, Ingelfinger and Belding³⁹ studied the motor function, intestinal absorption, pancreatic function and blood picture in 3 patients surviving total gastrectomy for three, five and ten years respectively. Two patients developed a macrocytic, hyperchromic anemia. The third had been receiving prophylactic liver treatment and had a normal blood picture. The pancreatic function and intestinal absorption were not particularly abnormal. The authors collected from the literature other cases of long survival following total gastrectomy. Apparently, ten and a half years for malignant and twenty years for benign lesions represented the longest survivals reported at the time of their investigation.

THE DUODENUM

Friesen et al⁴⁰ found gastroduodenal lesions or erosions, or both, complicating fractures of the long bones in 27 out of 1432 autopsies. Experimental work was carried out in animals and it was observed that similar lesions could be produced by operative fractures, curettage of the bone marrow and intravenous injection of small amounts of fat. The fractures did not increase gastric secretions or acidity. The authors believe that the ulcerations were produced by fat emboli which could be demonstrated microscopically in the mucosal and submucosal vessels of the stomach and duodenum. The emboli produced anemic areas in the mucosa, which became susceptible to the acid-peptic digestive activity of the normal gastric juice.

Meulengracht⁴⁴ presents his experience of fifteen years with the management of acute bleeding in gastric and duodenal ulcer. He stresses the importance of a full puree diet in all cases. Of 1031 patients treated 26 (2.5 per cent) died. Unfortunately, the patients are not subdivided into age groups

and the severity of the hemorrhage. He believes that patients should not be operated upon during or just after a hemorrhage and that operation may be considered if the patient is over forty years old, has persistent or repeated bleeding and has a definite ulcer by x-ray examination and if a competent surgeon is available.

Jones⁴² advocates early gastroscopy between the third and tenth days in hematemesis and melena when x-ray films fail to reveal the cause of bleeding. In 60 per cent of cases he found superficial acute ulcers. He states that persistence of pain associated with an ulcer that has bled is a serious omen, and that all his fatal cases came in this group. According to him it requires from 100 to 150 cc of blood to produce a tarry stool, and that 2000 cc of blood introduced into the upper gastrointestinal tract will produce bloody but never tarry stools. He recommends a semisolid puree diet similar to Meulengracht's. The mortality in Jones's series was 8 per cent.

Stewart et al⁴⁵ have recommended immediate operation on all patients with massive hematemesis and melena when there is good evidence that ulcer of the stomach or duodenum exists. Of 54 patients observed 33 were operated upon and the remainder used as controls since they or their physicians refused to consider surgery. Fifteen per cent of those operated upon died, whereas 29 per cent of those refusing operation succumbed. These patients were not given x-ray examinations prior to operation, and 4 of the 33 proved to be bleeding from other causes than ulcer and all these patients survived the exploration. The stomach was emptied of the blood clot by gastrotomy, and a radical subtotal gastrectomy was done, even if no definite ulcer was found. In 5 of these cases shallow ulcers with bleeding vessels were demonstrated. An average of 3600 cc of blood was used in the surgical group and 2040 cc in patients not having operation.

Warren and Lanman⁴⁶ have presented their experience with massive hemorrhage from gastric and duodenal ulcer in the West Roxbury Veterans Administration Hospital. They advocate urgent operation in patients over forty-five years of age who continue to bleed massively for more than twenty-four hours and in those who have bled massively and stopped bleeding but have shortly thereafter bled again. In patients with difficult duodenal ulcer, they have had good luck in a small number of resections with exclusion of the ulcer and with two-stage procedures.

Dunphy and Hoerr⁴⁵ discuss the problem of massively bleeding ulcers at the Peter Bent Brigham Hospital (Boston). They have limited their operations to patients who appeared to be actually bleeding to death. From 1940 to 1945 there were 117 patients with massive bleeding admitted, with a mortality of 7.6 per cent. In 1946 and 1947 there were 45 cases with 1 death. Of 6 patients operated

Lahey²⁷ has presented the experience in his clinic with stricture of the common bile duct. He stresses the importance of end-to-end anastomosis with preservation of the sphincter of Oddi. In many cases sufficient distal duct can be developed by mobilization of the duodenum and splitting of the head of the pancreas. A T tube is placed through a new longitudinal opening distal to the suture line and is left in situ for one year.

Cole et al²⁸ agree that end-to-end suture of remaining segments of duct gives the highest percentage of good results. When the distal segment was fibrosed and useless, as it often is, their best results followed a Roux Y hookup. A recent development they have made consists in constructing a new duct segment from jejunal mucosa. This may have possibilities, particularly if the newly constructed duct can be supported from within for a long time.

Longmire and Sanford²⁹ have utilized a new method of restoring continuity between the bile ducts and the gastrointestinal tract in 3 patients. In cases in which there is only scar tissue in the hilus of the liver and no available duct structure left that can be found, their operation may be applicable. The edge of the left lobe of the liver is resected. A bile duct is isolated, and this is transplanted into a loop of jejunum, which is further used to provide a cover for the raw surface of the liver. An enteroenterostomy is made between the two limbs of the jejunum.

Wilson and Gillespie³⁰ have reported the successful outcome on a patient with completely destroyed common bile ducts by the Longmire and Sanford method. A modification using the Roux Y anastomosis was considered preferable to the original technic.

Grindlay³¹ has made a significant contribution to this subject. Tubes of a certain type of polyethylene film are constructed to bridge defects in the common bile duct as well as other hollow viscera. Experimentally it appears that this substance is inert in the human tissues. Bile salts do not seem to adhere to the inner surface of these tubes, and it is believed that they may not become plugged as easily as vitallium or rubber. It is important to point out that the polyethylene film must be a certain variety, which will soon be available for surgical use. Many of the polyethylene films employed so extensively in industry have a chemical substance incorporated that will actually cause tissue reaction and scar formation. The shape and size of polyethylene tubes made for a specific purpose offer a great advantage. In 4 patients in whom we have used these tubes in our Roux Y procedure the results have so far been better than those by other methods. If the tube is 1 cm in diameter and can be held in place for many months, there is an excellent chance that scar-tissue constriction will not recur. There are naturally some

difficulties in keeping these tubes from leaving the hilus of the liver too soon. Loops of wire may be incorporated in the outer layers of the tube so that they may be held in place by nonabsorbable sutures.

Best³² again calls attention to the benefits derived from the use of dehydrocholic acid in preventing the deposit of bile salts in tubes that have been used for bile-duct reconstruction. He uses his so-called "biliary flush" of decholin, magnesium sulfate, cream or olive oil, nitroglycerin and atropine in all his cholecystectomies and common-duct explorations as well. Although this is a very useful method in postoperative common-duct stricture, it is a nuisance to the patient and is expensive and hardly seems justifiable as a routine after adequate gall-bladder and common-duct surgery.

THE STOMACH

Hamilton³³ calls attention to the development of gastric ulcer after deep x-ray therapy of the abdomen. In a group of 256 patients receiving more than 5000 r in the upper abdominal region as a part of the treatment for metastatic cancer of the testis, epigastric distress in two or three months developed in half the cases. In 35 of these patients gastric ulcer developed in a previously normal stomach.

This is confirmed by Bowers and Brick,³⁴ who have observed 6 patients with post-radiation gastric ulcer requiring surgical intervention. Three of these were operated upon for perforation, and 3 for massive hemorrhage, with recovery in all cases.

Marshall and Welch³⁵ have reviewed the Lahey Clinic experience with gastric ulcer for the period between 1936 and 1945. One hundred and thirty-one, or 16.4 per cent of 800 patients, were treated surgically. In this group there were 26 malignant ulcers (19.8 per cent). From this evidence the authors believe a more radical attitude should be accepted regarding the treatment of gastric ulcer. The results following resection for benign gastric ulcer were satisfactory, and no recurrent or anastomotic ulcers occurred in their cases. The operative mortality was 2.85 per cent.

An excellent article on the incidence of gastric cancer has been presented by Pack and McNeer.³⁶ Since this is not a reportable disease, it is not possible to obtain accurate figures for the United States. This lesion accounted for over 26,000 deaths in 1940, in this country. The reported incidence throughout the world varies directly with the economic status, the educational and medical facilities and the life expectancy of the community or country. Deaths reach the highest level in the age group between sixty-five and seventy. A most striking rise in the death rate from gastric cancer was noted among the Negro race. It appears to be slightly less prevalent among the Jewish race than it is in the non-Jewish population in European cities.

Sweet³⁷ reviews 86 patients with carcinoma invading the cardia and lower esophagus observed

Spackman⁵⁶ reports 5 additional cases of bowel obstruction following irradiation for pelvic carcinoma. He calls attention to the early hyperemia and edema of the ileum and sigmoid that are often seen, and believes that the late obstruction is due to resulting scar tissue.

THE COLON AND RECTUM

Swenson and Bill⁵⁷ have deduced from the study of 20 children with congenital Hirschsprung's disease that this lesion is due to an area of localized spasm in the low sigmoid. Careful x-ray examination will reveal the area of spasm accurately. After an operative procedure had been developed in animals, thought best adapted to resection of the spastic area and preservation of the sphincter in such cases, 3 children were successfully operated upon. The follow-up period is short, but the method promises to revolutionize the management of this troublesome malady.

Kiefer⁵⁸ tried all the "specific" methods of medical treatment known to him in ulcerative colitis. Sulfaguanidine benefited the greatest number of patients, but penicillin and sulfasuxidine were of most value in the preoperative and postoperative periods and for control of abscesses or peritonitis. In 527 cases followed for two or more years the results were satisfactory in 46 per cent. Medical management was successful in two thirds of the milder cases and in a third of the severe forms of the disease. Ninety-nine of 400 patients under observation for a long period were eventually operated on.

Vagotomy has been performed by Dennis⁵⁹ on 28 patients with ulcerative colitis or regional enteritis. Response to this indirect attack was successful in a high percentage of the patients so treated. The method is more adaptable to patients whose disease has not already produced extensive fibrosis and lack of distensibility of the bowel wall. The mechanism of this effect is in doubt, but the reduction in mucosal vascular response to intense emotional disturbances and relief of enteric spasm seem to be relevant. Vascular response to strong emotion can be observed through the sigmoidoscope in these patients, and it appears that such responses are no longer present after vagus-nerve interruption.

Cattell and Sachs⁶⁰ report that 26 per cent of 630 patients under treatment at the Lahey Clinic for ulcerative colitis were operated on. Ileostomy was performed in 145 cases, partial colectomy in 46, and total colectomy in 75. The operative mortality was 18, 15 and 4 per cent respectively in these procedures, with a total patient mortality of 22.3 per cent. Patients recently operated upon show a reduction in operative mortality to 4 per cent. The authors believe that when surgical intervention is necessary in ulcerative colitis, ileostomy will be required, and in most cases this procedure must be followed by removal of the colon.

On the basis of a recent study of 71 consecutive cases of ulcerative colitis, Best⁶¹ believes that approximately 90 per cent of these cases can be managed medically. In his opinion there is little evidence to support early ileostomy in the hope of arresting the disease so that restoration of continuity may eventually be carried out. Furthermore, he considers it better to have a few patients arrive too late for successful operation than to subject too many to permanent ileostomy.

Crohn, Garlock and Yarnis⁶² state that 8 per cent of their patients with idiopathic ulcerative colitis have right-sided lesions. There is a tendency to spread to the left side of the colon, and even when the rectum and sigmoid appear to be normal, fistulas and abscesses in the perirectal area develop. The authors have apparently had greater success with subtotal colectomy and ileostomy, with final re-establishment of ileosigmoidostomy, than other observers.

McKittrick⁶³ has presented an excellent treatise on carcinoma of the colon. The historical background is given, as well as a modern set of basic principles regarding the problem, as follows: the proper preparation of the patient for operation, optimum exposure of the segment of bowel to be excised, adequate mobilization of the bowel, adequate operation for cancer, free blood supply of both segments to be anastomosed, avoidance of tension on the suture line, and proximal complete temporary colostomy if adequacy of suture line or blood supply is in doubt. The surgical mortality in 90 patients operated upon between 1932 and 1941 was 11 per cent in comparison to 3.6 per cent in 110 with primary anastomosis operated upon between 1942 and 1947.

Jones, Robinson and Meads⁶⁴ report 137 consecutive combined abdominoperineal resections for carcinoma of the rectum and lower sigmoid without mortality. They attribute their lack of fatal complications largely to the use of alloy steel wire in abdominal-wound closure. The usual amount of urinary retention and bladder infections was obtained. Mild obstruction relieved by passage of a Miller-Abbott tube occurred in 9 per cent. There were only 2 cases of pulmonary infarction, and 4 of atelectasis. Wound infection occurred in 2 per cent of the cases.

Dixon⁶⁵ presents the results obtained in 426 cases in which anterior resections of the rectosigmoid and upper rectum, with primary anastomosis, were performed. A routine defunctioning transverse colostomy is done, and drainage is established to the sacral area through the lower end of the abdominal wound. Since chemotherapy was made available the operative mortality has been reduced from 5.9 to 2.6 per cent. In 272 patients the five-year survival was 67.7 per cent.

Wangensteen and Toon⁶⁶ review the results of low anastomosis after anterior resection. They

on in the first series 3 died, whereas in the last group 7 were operated upon, with no deaths

Baker⁴⁶ made a clinical study of 576 patients admitted to the Selly Oak Hospital (Birmingham, England) in the six-year period 1940-1945, with bleeding from gastric and duodenal ulcer. In this series the mortality was 14 per cent, whereas in a similar group admitted from 1934 to 1939 it was 7 per cent. The effect of the war on the psychic and economic situation is offered as an explanation of this discrepancy. The author believes that x-ray examination should be withheld during the acute phase, since recurrence of bleeding that resulted fatally was noted in 6 patients shortly after fluoroscopy.

A comparative study has been made by Allen⁴⁷ on two series of patients with uncomplicated duodenal ulcer. One group was treated by the standard partial gastrectomy, and the other by vagus-nerve resection. The results are considered on the immediate and interim basis, since many of the cases, particularly in the vagus-resection group, have not been followed sufficiently long to be classified as end results. The good results in both groups were approximately the same: 85 per cent in the gastric resections and 87 per cent in the vagus resections. The operative mortality was 2 per cent in the former as opposed to 0 in the latter. A similar study has been carried out by Warren and Meadows⁴⁸ on a smaller group of patients with almost identical findings.

Moore⁴⁹ gives a detailed analysis of 84 patients subjected to vagus resection. A strict grading revealed 75 per cent good results, 18 per cent fair results and 7 per cent poor results. Actually, the surgeon and the patient were reasonably well satisfied in 90 per cent of the cases. Sixty-two per cent of patients had diarrhea, which was of major importance in 14 per cent. Sixty-seven per cent had some sensation of fullness, which was major or continuing in 13 per cent. Incisional pain was serious in 3 per cent, and subsequent gastroenterostomy was necessary in 2 patients. The highest percentage of satisfactory results was found in patients subjected to vagus-nerve resection for anastomotic ulcer.

Colp et al.⁵⁰ made a comparative study on two groups of patients with duodenal ulcer. In one group 38 patients were subjected to partial gastrectomy only, and another group of 34 had vagotomy in addition. The added vagus resection did not increase the operative mortality (no deaths in the group), but definitely increased the morbidity. A higher incidence of achlorhydria was noted after the combined procedure.

Walters and his associates⁵¹ state that vagus-nerve section gave results that were inconstant, variable and in most cases unpredictable. The relief of pain after vagotomy was considered to be due to a release of gastric spasm and a reduction

in gastric acidity. Since one incident of unsuspected perforation of a duodenal ulcer occurred after vagus-nerve section, the authors deduced that the freedom from pain was unrelated to the healing of the ulcer.

It appears that the majority of surgeons dealing with a large number of patients believe that vagus-nerve resection should be used for the treatment of stomal ulcer if none of the antrum had been left behind at the initial resection. Also, the procedure should be evaluated when operation for uncomplicated, intractable ulcer is considered in patients under thirty years of age. It is definitely contraindicated for gastric ulcer, because it is never possible to be certain that the ulcer is benign. It is generally believed that vagus resection and gastroenterostomy are illogical since, as Faxon⁵² has suggested, gastrojejunal ulcers with gastrojejunal fistula might again become a common problem under such a regimen.

The clinical features and late results in 244 patients with gastrojejunal ulcer entering the Mayo Clinic between 1937 and 1948 are discussed by Priestly and Gibson.⁵³ The surgical mortality was 4 per cent. Subtotal gastrectomy with excision of the stomal ulcer gave satisfactory results in 87 per cent of the patients over a period of five to ten years. If a previous partial gastrectomy had been done the results with a higher resection were less satisfactory. The immediate results following vagotomy were good in 19 of 24 patients who had had previous partial gastrectomy and in 19 of 20 patients whose previous operation had been gastroenterostomy only.

THE SMALL INTESTINE

Ravitch⁵⁴ suggests the implantation of the ileum into the anus after total colectomy for benign lesions such as polyposis and ulcerative colitis. In 2 patients so treated after colectomy for ulcerative colitis, there was good sphincter control, and excoriation of the skin was not a problem.

Endometriosis as a cause of small-bowel obstruction is discussed by McGuff et al.⁵⁵ Obstruction occurred in 16 of 48 cases of endometriosis of the bowel observed at the Mayo Clinic between 1920 and 1946. The patients varied in age from thirty-one to fifty-four years, with an average of thirty-nine and a half. Although 15 of the 16 patients were treated by bowel resection the authors believe that ovarian ablation, preferably by operation with proximal decompression of the bowel, will result in complete resorption of the obstructive process. Although their premise may be sound, one doubts the advisability of such an indirect attack for localized obstructive lesions since the morbidity is greatly increased. Furthermore, it is well known that scar tissue resulting from endometriosis may produce obstruction of the bowel after ovarian function has ceased.

found 7 local recurrences in 51 cases (14 per cent) and state that these were outside the anastomotic area. Their patients had no difficulty with sphincter control and had normal sexual function.

Preparation and aftercare of patients on whom operations on the lower bowel have been performed is discussed by Bacon and Rowe.⁶⁷ A clean, tranquil bowel is desired, and this state may take several days of preparation. Sulfathiazole and streptomycin are advocated for only forty-eight to seventy-two hours preoperatively, because it is believed that the early effect can be depended upon but that reversion of action frequently occurs. A recent series of 142 cases without mortality is reported.

The urge for sphincter preservation may be on the wane. The number of local recurrences has been too great in the hands of most surgeons. Implantation of cancer cells into the suture line must be considered as a possible cause for recurrence. One is justified in preserving the sphincter in patients who have liver metastases and in those with very early lesions that can be adequately removed by any local procedure. Judgment based on experience plays a greater role in this situation than in many others.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M.D., *Editor*

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CASE 35211

PRESENTATION OF CASE

A sixty-five-year-old machinist was well until three months before admission, when he consulted his physician because of progressive weakness and a persistent upper respiratory infection. He had a "mild cough" productive of a small amount of mucoid sputum. There was no hemoptysis, no pain and no exertional dyspnea. Since the onset of his illness he noted difficulty in breathing during bad weather. For the two months preceding admission he was confined to bed. During this time his weakness progressed, and just prior to admission his sputum increased in amount. There was no history of fever, night sweats or wheezing. There was a 17-pound weight loss in these three months. In the month prior to admission he developed hoarseness and diminished hearing.

Physical examination on admission showed a dehydrated, cachectic and slightly cyanotic man. There was a cataract on the right, and posterior superior synechia with fixation of the right pupil. There was no gross loss of hearing. There was a palpable lymph node in the left supraclavicular fossa, and the trachea was markedly deviated to the left. There were hard movable lymph nodes, measuring 1 cm diameter or more, in both axillae. There was dullness to percussion posteriorly on the left below the level of the eighth rib, and bronchophony and absent breath sounds over the same area. The heart was normal in size, with a regular rate, and free of murmurs.

The temperature was 100° F, the pulse 90, and the respirations 30. The blood pressure was 88 systolic 64 diastolic.

Examination of the blood disclosed a hemoglobin of 12 gm and a white-cell count of 25,800, with

91 per cent neutrophils. Urinalysis was negative. A stool was guaiac negative. Blood culture was negative. Repeated sputums and gastric washings were negative for acid-fast organisms. The prothrombin time was 17 seconds (normal, 15 seconds). The nonprotein nitrogen was 19 mg, and the total protein 5.8 gm per 100 cc.

A chest film was reported as follows:

There is collapse of the left upper lobe and partial collapse of the left lower lobe. The mediastinum is shifted to the left. Within the collapsed segment, there are several fleecy densities and a suggestion of small punctate calcifications. The left costophrenic sinus is blunted, and the left leaf of the diaphragm is not visualized. There is also partial collapse of the right upper lobe, with irregular increase in density and punctate calcifications; also, there is some thickening of the overlying pleura. The right lower and right middle lobes are overexpanded, and they herniate into the left side of the chest anteriorly. The right leaf of the diaphragm moves freely and is elevated somewhat anteriorly. The patient was given a swallow of barium, and the esophagus showed no obstruction, although it was deviated to the left by the collapse on that side.

The patient's course in the hospital was febrile, the temperature varying between 99 and 104° F. At times he was disoriented and incoherent. An electroencephalogram was reported as a borderline record. A lumbar puncture showed normal pressure, and the spinal fluid was normal. Penicillin was given, with no effect on the febrile course. A chest film taken sixteen days following the first film was reported as follows:

The left chest is now entirely dense. A few air-containing areas shine through in the central portion that look like small abscessed cavities. How much of the density in the left side is due to consolidation, atelectasis, or drowned infiltration, or how much to fluid in the pleural sinus is not determinable. There are areas of infiltration in the right apex and first and second interspaces, with small areas of cavitation interspersed.

The patient's course remained febrile, and terminally respirations became rapid, and he died of respiratory failure on the thirty-eighth hospital day.

DIFFERENTIAL DIAGNOSIS

DR ARTHUR PIER. In summary, we have a sixty-five-year-old man who was perfectly well until recently, when he developed a cough, fatigue, weakness, weight loss and x-ray evidence of bronchial obstruction and pulmonary infiltration and then went rapidly downhill to die, with fever, leukocytosis and a low-grade anemia accompanying his hospital course. We do not get much information from the physical examination of the chest except to learn that there was disease present. I wonder

if we can look at the x-ray films I believe they were taken two weeks apart

DR STANLEY M WYMAN They show the mediastinum and heart to be displaced toward the left, with rather mottled density occupying the distribution of the left upper lobe and to a lesser extent in the left lower lobe. Unfortunately, the films are not penetrated sufficiently to outline the bronchi well, but on the second examination, one can trace the left main bronchus down to the region of the upper and lower lobe branches, at which point it is impossible to trace the bronchi farther. The multiple areas of infiltration in the collapsed right upper lobe are well seen, and there is definite calcification within them. I am not able to be certain of calcification in the left-lung field.

DR PIER Do you see any involvement of the mediastinum, or can you tell?

DR WYMAN It is impossible to see it adequately.

DR PIER Has there been any change in the right apex between the first and second films?

DR WYMAN There is a suggestion that there had been some added density in the lower portion of the diseased area. It does suggest a progression of some infiltrative or consolidating process.

DR PIER I must say that I am a little nonplussed by these films and a little less certain about the diagnosis than I was on reading the protocol because these calcified flecks in the right apex represent old, healed, burned-out tuberculosis. I cannot attach to them any further significance. I do not believe that tuberculosis was an active participant in the patient's very rapid decline.

Could he have had some bizarre infiltrative process in the lung such as a mycotic infection—for example, actinomycosis? It is my impression that actinomycosis, although often involving both lungs, usually involves the lower portions of the lungs rather than the upper. It is an invasive disease, which causes necrosis and small abscess formation and spreads relentlessly, without regard to any barrier through lung tissue, pleura and chest wall, creating on its way fistulas and sinus tracts. A patient with actinomycosis frequently raises large amounts of yellow sputum in which can be found the characteristic sulfur granules. I do not see any evidence here on which to base a diagnosis of actinomycosis or of any other mycotic infection.

Nor do I believe he had a necrotizing pneumonia. The onset was too insidious and the course was too long.

The history in a sixty-five-year-old man of cough, weight loss, bronchial obstruction and pulmonary collapse, with rapid deterioration leading to death, spells bronchiogenic carcinoma to me, and very little else. I am going to cling to that diagnosis although I am somewhat disturbed by the bilateral nature of this man's disease. I do not see why it could not have been bilateral if it had gone far enough. His symptoms and his course are more

consistent with bronchiogenic carcinoma than with anything else. His mucoid sputum, even though not bloody at any time, is characteristic of bronchial irritation and is often seen, in the early stages at least, in cases of bronchiogenic carcinoma. His fever, pronounced leukocytosis and low-grade anemia are also entirely compatible with a diagnosis of bronchiogenic carcinoma and are probably indicative of pulmonary infection peripheral to the obstruction. The early course of bronchiogenic carcinoma is often insidious and deceptive. Frequently, there are no noteworthy symptoms or signs until it is far advanced. Certainly, if that is what this man had, and I am sure it is, it was way out of possible therapeutic bounds by the time he developed outstanding symptoms.

It is perhaps a little academic for me to try to determine what type of cell his cancer arose from. The three types generally classified are the small-cell, or oat-cell carcinoma, the adenocarcinoma, and the epidermoid, or squamous-cell carcinoma.

The oat-cell, or small-cell type, is a very malignant variety that usually arises in or near the hilus and tends to invade the mediastinum, often getting tangled up with the aorta and great veins and often causing symptoms of mediastinal compression. It infiltrates lung tissue and metastasizes widely via the lymphatics to distant parts of the body—to the liver, lymph nodes, bone, adrenal glands, brain and other organs. It usually occurs in a somewhat younger age group than this man falls into. It is impossible to tell by looking at this patient's films whether the mediastinum was extensively involved or not. He developed hoarseness, however, and hoarseness implies involvement of the recurrent laryngeal nerve.

The adenocarcinomas usually arise somewhat more peripherally in the bronchial tree and form round masses and invade the lung tissue extensively and metastasize widely via the blood stream to the liver, opposite lung and brain.

The epidermoid, or squamous-cell, variety grows more slowly than the others, metastasizes less widely and is the most amenable to surgical resection. Like the other types it invades the lung tissue and spreads to the hilar lymph nodes.

Finally, there is a cell type that is so undifferentiated that it cannot be well classified.

All these carcinomas cause bronchial obstruction with atelectasis, damming-up of bronchial secretions and often pneumonitis, frank suppuration, and all the evidence of infection.

I think this patient had a very rapidly growing bronchiogenic carcinoma, probably of an undifferentiated variety and probably arising in the left-upper-lobe bronchus. I would guess that it also involved the left-lower-lobe bronchus and spread across the trachea to involve the right-upper-lobe bronchus. I think the left lung will be found to be extensively invaded by tumor, and I think there

was abscess formation secondary to this tumor invasion, partly from obstruction and partly, perhaps, from necrosis of the cancer itself. I rather think that a good deal of what we see in the right apex is tumor. A massive, left pleural effusion seems to have developed terminally and probably contributed to his death.

The only diagnosis I can make is bronchiogenic carcinoma, probably of an undifferentiated sort. I do not see any very good evidence for distant metastases except the lymph nodes in the axilla and supraclavicular region, which were undoubtedly involved. I do not think that we need to postulate adrenal or cerebral involvement to account for his relatively low blood pressure on the one hand and for his disorientation on the other. I think there could be nonspecific findings that might occur in any very sick, dehydrated, cachectic man.

DR JOSEPH C AUB: Dr Pier did better than we did on the ward.

DR TRACY B MALLORY: Do you want to discuss it?

DR AUB: No.

DR MALLORY: Does anyone want to take up the cudgels for tuberculosis?

DR HELEN PITTMAN: I took them up when Dr Aub showed me the films on the ward the other day.

DR LAMAR SOUTTER: It is worth commenting from the tuberculosis standpoint that one occasionally sees older people who have considerable tuberculosis without positive sputum. We had one such patient a few years ago with progressive collapse of one lung from whom several sputum specimens were examined but were never positive until the day before operation.

DR EDWARD B BENEDICT: I recall doing a bronchoscopy on an elderly man eight years ago. The gross appearance of the bronchi was consistent with cancer. The pathology report was tuberculosis, and I think we had seriously considered tuberculosis. But I must admit that we see both cancer and tuberculosis in the same patient.

DR J GORDON SCANNELL: Is it fair to ask if he was bronchoscoped?

DR BENEDICT: He was probably too sick.

CLINICAL DIAGNOSIS

Pulmonary tuberculosis

DR PIER'S DIAGNOSIS

Bronchiogenic carcinoma, undifferentiated, left upper-lobe bronchus, with involvement of entire left lung and apex of right lung

ANATOMICAL DIAGNOSES

Oat-cell carcinoma of left main bronchus, with metastases to brain, liver, adrenal gland and lymph nodes

Atelectasis, severe, left lung

Organizing pneumonia, slight focal, left lung

Pulmonary tuberculosis, chronic, active, right lung

PATHOLOGICAL DISCUSSION

DR MALLORY: Autopsy showed extensive carcinoma in the left main bronchus, which had spread extensively into the lung. The tumor was adherent to and narrowed by compression, both the aorta and the esophagus but did not invade either organ. The remainder of the left lung showed some foci of old organizing pneumonia and almost complete atelectasis. There was no fluid in the pleural cavity, and the apparent consolidation was due to complete absence of air in the pulmonary parenchyma. There was extensive old tuberculosis at the right apex, and other foci in the right lung, which were not entirely inactive. Some fresh tubercle formation was found, and it is quite conceivable that he might have shown positive sputum, from time to time. The tumor had metastasized very widely. The bronchial lymph nodes and nearly all the retroperitoneal peripheral nodes were involved. There were metastases in the liver and one in the adrenal gland, but the most notable metastases were in the brain, where some forty or fifty small separate tumor nodules were found widely scattered through all parts of the brain cortex, white matter and the cerebellum, but were not of sufficient size to have produced localizing symptoms.

DR AUB: What kind of tumor was it?

DR MALLORY: An oat-cell carcinoma.

DR PITTMAN: Was the disease on the right all tuberculosis?

DR MALLORY: Yes, there was no tumor there.

CASE 35212

PRESENTATION OF CASE

First admission. A fifty-six-year-old Russian physician was admitted for diagnosis and treatment of a lung tumor.

Twenty-seven years before this admission he was treated with bed rest for six months because of tuberculosis in the left upper lung. Nine years before this admission while he was being routinely fluoroscoped, a lesion the size of a dime was detected in the same location as the previous tuberculous infection. At this time he was practicing medicine and was symptom free. Six years before this admission, while he was having a gastric series, during the investigation of a possible duodenal ulcer, the chest lesion was seen again now the size of a quarter. Many x-ray films were taken until three years before admission, when the patient decided to forget the whole matter. These films were all available for examination when he was admitted to this hospital. Some of them taken about four or five years before

admission showed definite regression in size of the lesion until it was about the same size or even smaller than when found originally nine years previously. The decrease in size was a shrinkage of the shadow, rather than a central destruction. The lesion then (three or four years before entry) returned to the same size or larger than it had been six years before entry.

Two months before admission he had a short illness accompanied by chills, fever and blood-streaked sputum for one day only. An x-ray examination showed still further enlargement of the lung lesion. There was no chest pain, dyspnea, joint symptoms, weight loss or loss of appetite. He did have occasional bouts of productive coughing.

The temperature, pulse and respirations were normal. The blood pressure was 130 systolic, 90 diastolic. Physical examination was negative. The hemoglobin was 14.6 gm, and the white-cell count 6800, and urinalysis was negative. Sputum examination was negative for acid-fast bacilli.

A chest x-ray examination was reported as follows:

Lying in the left mid-lung field in the anterior segment of the left upper lobe is a lobulated homogeneous mass approximately 5.0 by 4.8 by 6.0 cm, in which no calcification is recognized. The superior portion of this mass shows an



FIGURE 1

unusual degree of lobulation. The lesion lies in intimate contact with the minor fissure, separating the left-upper from an anomalous left-middle lobe (Fig. 1). There is no apparent extension through the fissure, and the lung fields appear clear, except for a few calcified scars in the upper-lung fields. Definite hilar or mediastinal lymph nodes are not recognized, although there is a suggestion of an ill-defined similar density just above the left main bronchus. Spot films of the lesion

show a suggestion of a division of the mass into possibly three component parts, the strongest suggestion being in the upper portion. A review of previous films shows the superior and lateral portions of the mass to be of more recent origin than the medial lower portion.

Exploratory thoracotomy was proposed but the patient left the hospital to settle his affairs.

Second admission (two and a half months later). The patient continued to have a cough with sputum and occasional blood streaking. On a repeat chest x-ray examination it was reported that "the superior lobulation of the mass appears to be slightly larger than at the last examination, otherwise there is little if any change." The sputum was again negative for acid-fast bacilli. On the seventh hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. RICHARD SCHATZKI: The record mentions a series of films dating back nine years prior to admission. These films are not available now. I would like to see the films and not take someone else's word for them. I will have to do so, and for the sake of this exercise I will assume that the interpretation was correct and did not show any more than is given in the record.

I will start with the x-ray films. There is very little I can add to the description as given in the record. There are two striking features about this mass. One is the marked lobulation. It is really segmentation, as if the mass had originated from more than one place, possibly, it arose from more than one focus. Another interesting feature is the fact that the point of attachment of the mass, at this anomalous fissure between the left middle and upper lobes, shows surprisingly little if any bulging. The second striking thing about this mass is its duration, if we can assume that what we see now has been present for at least nine years. The mass is reported to have markedly decreased in size at one time, and to have increased again. It is also a mass that had in no way handicapped the general well-being of the person who had it. That is a rather unusual story. If one did not have the history and just looked at the films, things would be much easier. I should like to ask one or two questions, which are not in the record, in order to exclude certain things, which I think can be excluded fairly rapidly. There is no differential count mentioned. How many eosinophils were there?

DR. TRACY B. MALLORY: None.

DR. SCHATZKI: No blood Hinton test is mentioned.

DR. MALLORY: I can find no record of that. Do you remember, Dr. Scannell?

DR. J. GORDON SCANNELL: I do not, but I assume it was negative.

DR. SCHATZKI: That is enough.

There are numerous lesions that might occasionally produce a shadow in the lung, as this one did. I am not going to enumerate all of them. I will mention a few likelier ones rather than other

rarer ones. There are four conditions, if we exclude echinococcal cyst and the very rare gumma of the lung, which conceivably could produce such a picture and such a history. A bronchiogenic cyst would explain the fluctuation in size, which occurred during observation. It is very difficult to explain the appearance of the lesion on that because of the marked lobulation. I do not remember having seen or heard of a segmented bronchiogenic cyst. It is conceivable but so unlikely that I will exclude the possibility. The second is benign adenoma in the periphery of the lung. Benign adenoma occurs practically always in the large bronchi. It rarely occurs in the periphery, but we have seen in these exercises at least 2 cases in which benign adenoma did occur in the periphery of the lung. In favor of it would be the marked lobulation. The shape would be consistent. The absence of any appreciable amount of atelectasis — in the last film a small amount is visible — and the rather recent clinical history make me believe that it is not so very probable. I put particular stress on the definite decrease in the size of the lesion, which we are going to take for granted. If we exclude these possibilities, there are two left that are uppermost in our minds: primary malignant tumor of the lung and tuberculoma. The history, of course, points very strongly toward the latter possibility. Could this have been a tuberculoma? The present x-ray appearance is consistent with a diagnosis of tuberculoma, although it is a little different from the tuberculomas that I remember having seen. It is unusual for tuberculoma to have such a sharp edge. Usually there is some scarring or small area of atelectasis, which produces the appearance seen in the corona of the sun. But I can conceive that this does not always have to be so, and it may be tuberculoma. How about the history? I have seen a case in which a tuberculoma grew under observation and was proved by operation. It would be a little more difficult to see how a tuberculoma could shrink and then start to grow again. As a matter of fact that statement is unusual for anything I can think of.

The last possibility I am going to discuss is that of malignant tumor of the lung. Could this have been a bronchiogenic carcinoma of the lung? If we had x-ray films alone and no history this would be our first bet. It is a little difficult to reconcile the history with this diagnosis. Can someone have bronchiogenic carcinoma for nine years, and have no more symptoms than this man had? Certainly I have never seen one, although I can conceive that it might be possible. Bronchiogenic carcinoma is a more slowly growing carcinoma than we usually assume. However, it is difficult to see how bronchiogenic carcinoma could decrease in size without evidence of ulceration, and one would be forced to make two diagnoses. I would say that my choice is between tuberculoma and malignant tumor in the lung. If the two lesions are the same it will have to be tuberculoma. If it just happens to be in the

area where the patient had had old tuberculosis, I would make bronchiogenic carcinoma my first bet. For the record's sake I have to choose one of the two, and I shall therefore take bronchiogenic carcinoma as my first choice, and tuberculoma as my second.

DR JOSEPH C. AUB: I am surprised at that diagnosis. The record states that this lesion was situated between two lobes and from here it looks like a cyst. The patient came from Russia even though he did not have a high eosinophil count. Why could it not have been a hydatid cyst, since it lay between the two lobes?

DR SCHATZKI: When I read the record without seeing the films, I made a diagnosis of echinococcal cyst. When I saw the films, I still thought it could be an echinococcal cyst. If I had been the clinician I would have done all that was necessary to rule that possibility out, I could not do that here. The only thing I could ask for here was the eosinophil count because I realized I would not get an answer if I asked for the result of a complement-fixation test for echinococcus. For that reason I had to exclude it from my differential diagnosis. I agree, from the history, that it could be, however.

DR AUB: Does the mass lie between the two lobes?

DR SCHATZKI: No, I would say it lies in the lobe.

DR ALFRED KRANES: Is it possible that the repeated chest x-ray examinations that he had would affect a sensitive tumor?

DR SCHATZKI: Not the amount he apparently had.

DR EDWARD B. BENEDICT: Was a bronchoscopy done?

DR SCANNELL: No.

DR BENEDICT: Was there any reason for not doing one?

DR SCANNELL: Yes, because of the peripheral nature of the lesion. Opinion was divided into two camps. We joined the camp that thought he ought to be operated on.

DR BENEDICT: I agree that he certainly had to be treated as a cancer patient, but I would have bronchoscoped him on the chance of finding a finger-like process in the left-upper-lobe bronchus with a right-angle bronchoscope and obtaining washings for a cytologic study. Even if it were negative, I would still explore.

DR SCANNELL: That was our viewpoint. We did not see how it would change the therapy.

DR LOWREY F. DAVENPORT: I would like to ask a general question. The statement has been made that on a percentage basis peripheral tumors are more apt to be adenocarcinoma. Dr Siegfried J. Thannhauser called my attention to the fact that he was certain that the ones that shelled out forming abscesses were more apt to be epidermoid than adenocarcinoma. What would you say to that as a differential point in the case of a solitary tumor in the periphery of the lung?

DR MALLORY Most of our abscesses have been either with epidermoid or with oat-cell tumors, rather than adenocarcinomas

DR STANLEY M WYMAN It is worth stating, as the record says, that careful review of the old films convinced us, at least, that the nodule had been in the same location from the first examination, and represented a part of the mass that we now see

DR SCANNELL My impression is that a complement-fixation test was done before he came here and was negative. He was Russian born, but had lived in South Africa for twenty years. He had had the whole gamut of studies done by all his medical friends every place he went. Our opinion as we stood at the operating table was similar to Dr Schatzki's. Before we operated Dr Edward D Churchill, at least, said that he thought it was a tuberculoma, and we were prepared to give streptomycin. On opening the chest we found a complete left middle lobe, and in the anterior segment of the left upper lobe was a puckered area with an underlying mass, no overlying pleural adhesions and very little injection of the surrounding lung or pleura. A left upper lobectomy was done. A biopsy was also taken since we believed at that point that it was probably tumor rather than tuberculoma. There were no involved lymph nodes, and the hilar areas were clear. There were minimal adhesions at the left apex.

CLINICAL DIAGNOSIS

Tuberculoma?

DR SCHATZKI'S DIAGNOSIS

Bronchiogenic carcinoma?
Tuberculoma?

ANATOMICAL DIAGNOSIS

Adenocarcinoma, left-upper-lobe bronchus

PATHOLOGICAL DISCUSSION

DR MALLORY The specimen we received showed a lobular, very sharply circumscribed but nonencapsulated tumor, which, on microscopical examination, proved to be a very well differentiated adenocarcinoma. Portions of the tumor were, in my opinion, better differentiated than any cancer of the lung that we have ever seen, and yet there can be no doubt about its malignancy. It appeared to be still relatively slowly growing, and I believe the tumor could have been present for a large part of the recorded history. We did not find any other lesion that would explain the previous shrinkage of the shadow.

DR SCHATZKI Do you have any explanation how that might occur?

DR MALLORY No, I have not. This was an extremely solid tumor, rather scirrhous, in fact, which is unusual in a pulmonary tumor, and it is very hard for me to see how it could have shrunk.

DR BENJAMIN CASTLEMAN The scirrhous character might mean that there had been previous necrosis of the tumor, which had caused it to shrink.

DR MALLORY It is possible, but there are so many sclerosing tumors in which one has no such evidence of episodes of necrosis that I do not think we can draw such a conclusion safely.

DR SOUTTER What is the possibility of a metastatic adenocarcinoma?

DR MALLORY I cannot rule out that possibility.

DR SCANNELL That was probably ruled out clinically from previous studies. The tests were not done here, but barium studies and pyelograms carried out elsewhere were all negative.

DR MALLORY The tumor involved the entire bronchial segment and was growing into the lumen of the bronchus in a fashion characteristic of primary tumor. Of course we do know that metastatic tumors occasionally grow intraluminally.

DR SCHATZKI What caused the extreme segmentation—just the shape of the tumor?

DR MALLORY Yes

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AMERICAN ACADEMY OF GENERAL PRACTICE

THE first annual clinical meeting of the Massachusetts Chapter of the American Academy of General Practice, which was held in Boston on April 15, not only represents the growing extension of chapters of the Academy (which have been formed in almost all the states) but also recalls the principles and goals of the organization. The purposes of the Academy, as stated in its constitution, are as follows: to promote and maintain high standards of general practice of medicine and surgery, to encourage and assist young physicians in preparing, qualifying and establishing themselves in general practice, to protect the right of the general practitioner to engage in medical and surgical procedures for which he is qualified by training and ex-

perience, to assist in providing postgraduate study for general practitioners and to encourage and assist physicians and surgeons to participate in this training and to advance medical science and private and public health. The Academy at present has a membership of more than 10,000, and the potential membership includes more than 100,000 general practitioners.*

The officers of the Massachusetts Chapter include Dr. John R. Fowler, of Spencer, as president, Dr. Lewis S. Karp, of Worcester, as vice-president, and Dr. James G. Simmons, of Fitchburg, as secretary-treasurer. The directors are Dr. Nathaniel N. Bennett, of Springfield, Dr. Harold F. Brown, of Brookline, and Dr. Fred L. Campbell, of Brighton. The activities of the first annual meeting comprised ward rounds, clinics and lectures on such varied subjects as psychosomatic illness, premarital counseling, the Rh factor, hypertension and virus diseases, all presented with particular attention to the interests of the general practitioners.

At the first scientific assembly of the Academy, held in Cincinnati early in March, the attendance was more than twice the number that had been anticipated. Meetings of the various chapters have evoked a similar interest.

The Academy, which represents at once the oldest of the medical arts and the newest of the specialties, is the result of a conviction among groups of general practitioners in several states that progress in medicine and surgery is basic to the welfare of the people and, incidentally, of the medical profession. As he takes his place among his fellows in more dramatic (and often more remunerative) specialties, the general practitioner epitomizes the best and most familiar aspects of medical practice. His role of healer, counselor and friend in time of need is a bulwark against interference with the free practice of medicine.

*First scientific assembly is outstanding success. *Gen. Practice News* 21 April 1949

"FETUS AND NEWBORN"

THE strength of a nation may be said to depend primarily on the care and training of its young. Such a statement, no doubt true, can nevertheless be variously interpreted. In the city-state of Sparta

artificial means were added to the method of natural selection the weak infants were exposed upon the hillsides, and only the strong survived to be subjected to the rigid discipline of the nation. Under conditions imposed at the highest levels of modern civilization, total survival is sought, for better or for worse, with quality to be attained through environmental influences rather than by the processes of natural selection.

In this country, still devoted to humanitarianism, every effort, come what may, is bent toward both the preservation and the betterment of life.

The American Academy of Pediatrics, in a relatively short existence, has already made two important contributions to child care. The second of these, the recently completed Study of Child Health Services, is already notable as the most exhaustive inquiry that has yet been made into the pediatric resources of the country, the earlier and continuing study, the work of the Academy's Committee on Fetus and Newborn, less ambitious in scope and less widely publicized, is nevertheless hardly of less importance.

In 1943 the Committee on Fetus and Newborn, working with the Children's Bureau, assisted in developing "Publication 292" of the Bureau — its manual, *Standards and Recommendations for the Hospital Care of Newborn Infants — Full-Term and Premature*. Continuing its program of developing and improving facilities for the hospital care of newborn infants and aided by state groups covering the entire country, the Committee, under the chairmanship of Dr. Stewart H. Clifford, of Boston, last fall presented its completed manual.

This manual, as its title implies, embodies a most acceptable and inclusive set of standards for the hospital care of newborn infants. It is particularly timely at a period during which deficiencies in hospital personnel have combined with an increased popularity of hospital lying-in to make the risks of neonatal infection a very real hazard.

No hospital that offers obstetric facilities can afford to operate its nursery along lines other than those established by the committee. In this instance the benefits of uniform procedure far outweigh its disadvantages.

MENE MENE

THE New York County Medical Society, which last winter "disapproved" the assessment and twelve-point program of the American Medical Association, has seen new writing on the wall. Repenting of the stand taken by a militant minority of the membership at the earlier session, a "huge attendance" at a later meeting on March 28 reversed the previous vote and recorded overwhelming approval of the present policies of the national association.

The general trend on the part of physicians is in the direction of adoption of the principles and acceptance of the program of the American Medical Association. Distrustful of the Association's conservatism, which has at times amounted to reaction, a number of its fellows at first hesitated to subscribe to its rejuvenated policies. These physicians, convinced of its integrity, are now joining the ranks in increasing numbers. A few, doubters to the last or devoted to the principles of paternalism in government, will never join. In general it may be said that the profession is presenting a stronger, more united front against the political control of medicine.

PRIZE ESSAY CONTEST

The *Journal* announces with pleasure the selection of the essay on Preventive Medicine by Miss Miriam D. Manning, a fourth-year student at Tufts College Medical School, as the winner of its 1949 prize essay contest. Miss Manning's essay will be published as the Medical Progress report on June 30. The prize was \$100.00. The second prize, consisting of a two years' subscription to the *Journal*, was won by Miss Suzanne Agnew, a member of the graduating class at the University of Minnesota Medical School.

The subject chosen for the next competition is "Recent Advances in the Study of Poliomyelitis." The conditions are the same as those that were published for the contest recently ended.

Manuscripts are to be between four and five thousand words in length, clearly typewritten in English, double or triple spaced with references listed at the end in numerical arrangement according to the form used by the *Quarterly Cumulative Index Medicus*. They must be in the hands of

the editor by March 15, 1950. All manuscripts will become the property of the *Journal*.

A cash prize of \$100.00 will be paid for the best essay of those found to be suitable for consideration, the paper will be published in the "Medical Progress" series that forms a regular part of the contents of the *Journal*, and the author will receive a hundred free reprints.

A second prize will consist of a two-year subscription to the *Journal*.

The editors wish to emphasize that in establishing this competition they are as much interested in encouraging good medical writing as they are in promoting the collection of scientific material. In judging papers that may be submitted, particular attention will accordingly be paid to clarity, simplicity and general literary excellence.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

DOBSON — William M. Dobson, M.D., formerly of Northampton, died on May 4. He was in his sixty-seventh year.

Dr. Dobson received his degree from Tufts College Medical School in 1907. He was a member of the American Psychiatric Association and the New England Society of Psychiatry. Two daughters and a sister survive.

DORION — Kinton F. Dorion, M.D., of Lawrence, died on January 29. He was in his seventy-fourth year.

Dr. Dorion received his degree from Laval University in 1902. He was a fellow of the American Medical Association. His widow, two daughters and a son survive.

GWINNELL — Alfred W. Gwinnell, M.D., of Boston, died on May 3. He was in his seventy-second year.

Dr. Gwinnell received his degree from Tufts College Medical School in 1911.

LOUGHRAN — James F. Loughran, M.D., of Lowell, died on April 17. He was in his eightieth year.

Dr. Loughran received his degree from Harvard Medical School in 1896.

Three sons and a sister survive.

MURPHY — John M. Murphy, M.D., of Brockton, died on April 24. He was in his sixty-eighth year.

Dr. Murphy received his degree from Tufts College Medical School in 1906. He was a fellow of the American Medical Association.

His widow, a son, a brother and two sisters survive.

SULLIVAN — John A. Sullivan, M.D., formerly of Pittsfield, died on April 8. He was in his sixty-fourth year.

Dr. Sullivan received his degree from Albany Medical College in 1910. He was a fellow of the American College of Surgeons and the American Medical Association.

His widow, a brother and two nephews survive.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATH

RONDINELLA — Annina C. Rondinella, M.D., of Wellesley, Massachusetts, died on March 11. She was in her seventy-sixth year.

Dr. Rondinella received her degree from Woman's Medical College of Pennsylvania in 1899, and was assistant dean for several years. She was formerly a member of the medical departments at Vassar College and Connecticut College for Women and was consulting ophthalmologist emerita at Wellesley College. She was a fellow of the American Medical Association and a member of the Association for the Advancement of Science.

A brother and two nieces survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The June schedule for Consultation Clinics for Crippled Children in Massachusetts under the provision of the Social Security Act follows:

CLINIC	DATE	CONSULTANT
Haverhill	June 1	William T. Green
Lowell	June 3	Albert H. Brewster
Salem	June 13	Paul W. Hugenberger
Pittsfield	June 15	Frank A. Slowick
Worcester	June 17	John W. O'Meara
Springfield	June 21	Garry deN. Hough, Jr.
Hannis	June 23	Paul L. Norton
Brockton	June 23	George W. Van Gorder
Fall River	June 27	David S. Grice

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

SCHOOL MEDICINE IN MASSACHUSETTS

To no one are the deficiencies of school medical services more acutely a source of vexation than to the average school physician. Most school physicians, sooner or later, experience a sense of frustration and aimlessness regarding the methods and objectives of their school work, though often at the outset of their incumbency they may have high enthusiasm. School physicians are public-health officers, therefore, it is the responsibility of those who develop public-health policies to aid in working out a plan by which the health requirements of school children can be better understood and satisfied and by which the special health potentialities of medical services in these large groups of school children can be better utilized than hitherto by the physician directing each school health program. It will be necessary to provide some money — necessary perhaps to conduct a demonstration program in some selected school area, and necessary to seek the more active co-operation of the Massachusetts Medical Society. Since school medical inspections were initiated in this country, right here in Boston, when in 1894 the city was faced with a severe epidemic of the dreaded diphtheria, the improvement of school medical services should be of special interest in Massachusetts. One resolution announced by the Panel on School Health at the recent Massachusetts Health Conference favored the development of a section on school health by the Massachusetts Medical Society. The development of such a section should receive consideration.

To work for a brighter future, it is not necessary to lay the blame on the past, whether the dissatisfying experience was the result of low salaries or the low salaries the result of dissatisfying experience. The fault appears to lie with all who failed to realize until quite recently that school medicine has greater

possibilities than the mere duplication and underwriting of the work of the general practitioner. Strangely enough, the most suggestive, stimulating and penetrative analyses of school health possibilities have by no means all emanated from the medical profession. An example of this is the American Child Health Association, of which Herbert Hoover was president, which published in 1925 its health survey of eighty-six cities and later that of seventy cities and finally, before its liquidation, published the study known as *Physical Defects Pathways to correction*.

Supported partly by funds from the liquidating committee of the American Child Health Association, partly by the Metropolitan Life Insurance Company and the Milbank Memorial Fund and by Social Security funds from the Children's Bureau, a fourth study known as the Astoria Demonstration Study was completed in a borough of New York City. These surveys provided much that was suggestive and constructive, and it is regrettable that the published reports are not more widely read.

Not until quite recently, however, has it become apparent that at least two, and probably three, wide fields are especially open to school medical practice. These are emotional health, child health education (I think I should also include adult education in child health), and studies of physical growth and the significance of deviations from standards, studies designed for use in large groups. Examples of such standards are the grids and graphs based upon various semiannual or more frequent measurements. In no way do I mean to imply that present activities of the school physician are to be abandoned. The search for physical defects and their correction and the prevention of communicable disease will not be less, but the physician's activities in the field of emotional health and of health education will be a great deal more.

Recognition of the importance of emotional health and the influences by which a child's emotions are swayed or damaged has not come too soon. Most parents are little aware of the importance of heedless acts or even inopportune absences upon the emotional health of their children. It is extremely important that parents be educated to an appreciation of these influences to prevent hurts that they do not wish to inflict. The problems of the child, whether physical or emotional, are best handled through prevention. It is a long hard row to rehabilitate a child with a tuberculous hip. How much better to prevent by eliminating the source. It is perhaps a longer and harder task to reclaim a happy and productive social being from an emotionally damaged child or — even worse — from the chronic delinquent.

The number of children and adolescents whose potential achievements are limited and crippled by emotional ill health is known to be extremely

large. Emotional ill health is, in fact, the most common disease of the white race. Who has not suffered from its effects? What a huge loss to Society this disease entails! How many Lincolns, Holmeses or Churchills have sought the solitude of lesser fields rather than public life, because of emotional crippling! One speaks nowadays of "total health" meaning not merely the absence of detectable physical disease but also the full enjoyment of all the potentialities with which a person was endowed at birth.

The prevention of emotional ill health is a yet unappreciated gigantic task. It is to be obtained through education, not only of the child but also, even more especially, of its parents. Of the available community resources, especially since the curtailment of state child-guidance centers or clinics, the school physician, aided by alert and sympathetic teachers, nurses and counsellors, has the finest opportunity to provide such education.

We are thus upon the threshold of the second field of normal school health service — that of health education. By this I do not mean that the school physician should embark upon formal education. That function he should leave to trained educators. But he can teach by example during his examinations, inspections and other contacts with children and teachers as well, and should explain, as he proceeds, what he does and why he does it. He will also seek every opportunity to educate — the child by example and the parent, the teacher and the nurse by lectures and personal talks.

On the other hand, direction of the much more highly developed preventive aspects of the school health program will require a man who will know how to teach by example, who will know how environment can affect child health, who will know how to cope with an unfavorable environment and who will explain to parents their true relations to the emotional health of their children. Such responsibilities, which will require special training, can only mean that the practice of school health will be recognized as a specialty. The specialty has already been named by others, and its representatives are styled "pediatrician psychiatrists." Medical schools already furnish instruction designed to cover this field, but few men so equipped are yet available.

There are other reasons for a radical change in the type of school medical adviser who today is usually a man engaged also in general practice, and of these none is more important than the conflicting demands of his school health duties with those of general practice. It must be acknowledged, I think, that even today the proper demands of the school health program are incompatible with general practice. The hours of the school day will be none too long for the demands upon the school physician. An ideal school health program cannot permit the urgent demands of obstetrics, sur-

gery or other emergencies to interfere with the essentially regular school medical work. Furthermore, there is the problem of an adequate salary.

While discussing the problem of providing a trained, full-time school physician with the Board of a neighboring city, one of the Board members stated, "Why! Such a physician would require a salary of ten to twelve thousand dollars! It is more than we pay our superintendent. Your idea is impracticable." It is true that a pediatrician-psychiatrist school physician would expect to make twelve thousand dollars. But is that price too high? Is it not rather that the community has for many years indulged in the practice, so far as schools are concerned, of expecting too much for too little? It is also true that although the practice of school health is incompatible with general practice, with its demanding emergencies, there is no reason why the hours or interests of school work should prevent a substantial and remunerative consultative practice so that to the specialist a salary considerably less than twelve thousand dollars, since it is to be only a part of his income, would be attractive.

Some say that the general services of the full-time, trained staff of the organized communities are the answer to this problem. My own opinion is that one must look forward to such clinical facilities in rural communities—and be fortunate indeed to obtain them—as the best solution in areas of low resources. But I believe that the school needs its specialist physician—one who has the responsibility of school work at heart, who has the special interest in school children that is necessary, who will watch his children at play and at work, who will know their parents and their special problems, and who will have studied the school environment including each teacher and other school personnel. If it is objected that the average school population is too large for such detail, I shall answer that the large school population requires that the physician recognize his responsibility so to train the teacher's observation that he can count on her efficiency, so that he may delegate to her much of the important function of screening her pupils and concentrate himself upon those most in need of his study.

Shall one attempt to place a figure of value in dollars against the loss to society not by death, which has been estimated elsewhere, but by emotional ill health whether or not it is followed by delinquency? I believe that six or even twelve thousand dollars is a modest fee to pay for the means of helping to prevent such crippling, which is annually produced in any city.

It is hardly necessary to say that a sudden change from present methods to school medicine administered by a specialist is not to be expected. However, the future is not without promise. The Commissioner of Public Health in Massachusetts has an active interest in the development of better school medicine. At present the postgraduate ed-

ucation of physicians concerned with school work seems the most promising line of attack. An example of such education is the course first given last year, under the sponsorship by the Department of Public Health with the co-operation of the Harvard School of Public Health.

Such a course will probably be given annually. It is limited to forty participants. Interest on the part of school physicians is indicated by the fact that applications for most of these forty chairs were received this year within three weeks of the time of announcement, one from as far away as North Adams, one from Northampton and one from Greenfield.

ALLAN R. CUNNINGHAM, M.D.
Consultant in School Health

MISCELLANY

ISRAELI MEDICAL SCHOOL

The Hebrew University-Hadassah Medical School, the first medical school to be established in the new State of Israel, opened its doors May 17, 1949, as a joint undertaking of the Hebrew University and Hadassah, the Women's Zionist Organization of America. Until security conditions permit continuation of construction on Mt. Scopus, the site of the present 400-bed Rothschild-Hadassah-University Hospital, the School will be housed in four hospital units, totaling initially over 300 beds, in the city of Jerusalem proper.

UNIVERSITY PROFESSOR

Dr Edwin J. Cohn, professor of biological chemistry in the Harvard Medical School and chairman of the Division of Medical Sciences in the Faculty of Arts and Sciences, has been appointed one of the four University Professors of Harvard University.

Long recognized for his work on proteins and the fractionation of blood, Dr Cohn now becomes one of the four scholars of the University 'especially chosen for work on the frontiers of knowledge'.

CORRESPONDENCE

PUBLIC RELATIONS THAT MAY BACKFIRE

To the Editor: In the annual report for the year ending March 31, 1949, of The Institute of Living at Hartford, Connecticut, the psychiatrist-in-chief, Dr Burlingham, discusses at some length what has been happening to psychiatry from publicity. A few quotations from this will give a very good idea of what Dr Burlingham thinks of the effects of ill advised publicity on psychiatry. These quotations follow:

When psychiatrists emerged from comparative obscurity a few decades ago, they had high hopes as to what could be accomplished in the sphere of public relations and education. Their objectives were to awaken the public to the long-neglected needs of the mentally ill.

Regardless of where the responsibility rests, the facts are that hordes of people are being given the impression that they need the services of psychiatrists, they are then being advised that the shortage of psychiatrists makes it quite impossible for them to get psychiatric help. They are being warned that one out of twenty-five per-

sons will wind up in a mental hospital, they are being presented with the terrifying picture of the horrible conditions in mental hospitals. Something should be done to stop this onslaught of injudicious publicity, or at least to disidentify it from scientific psychiatry. Publicity is a two-edged sword, publicity accidents are as common as publicity successes. It is absolutely necessary for us to be conservative and modest in all of our public statements. Overemphasis and overclaiming are inevitably followed by loss of public confidence and respect, which often as not manifests itself in ridicule and satire. Symptoms are already evident that such a reaction to psychiatry is setting in. We must ask ourselves if the efforts to arouse the public have gone out of balance.

As I read the constant inflow of pamphlets and letters and listen to the radio extolling the virtues of this or that medical project, I am impressed by their frequent overstatements, particularly the overenthusiastic claims, often being made. The idea for example is being given to the public that, if only enough money is given, the important problems of the cause and cure of many diseases surely will be solved, or that all that is needed to this end is the construction of new institute buildings or more hospital beds for research. A sort of dreamland of obliteration of suffering from disease seems in creation by these statements, but I wonder if there will not be an awakening from such dreamlands of publicity, if there will not come a future backfire from them as has seemingly come in the field of psychiatry. I fear that this may happen, and so I think it behooves organizing publicity campaigns for medical projects to be more cautious in their statements and promises than they now are.

HENRY A. CHRISTIAN, M.D.

20 Chapel Street
Brookline, Massachusetts

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Diseases of the Nose and Throat. A Textbook for Students and Practitioners. By Sir St. Clair Thompson, M.D., F.R.C.P. (London), F.R.C.S. (England), L.L.D. (Hon.) (Winnipeg), and V.E. Negus, M.S. (London), F.R.C.S. (England), surgeon for diseases of the throat, nose and ear, King's College Hospital. 8°, cloth, 1004 pp., with 44 plates, 13 in color, and 369 illustrations. Fifth edition. New York: Appleton-Century-Crofts, Incorporated, 1949. \$16.00.

This standard textbook was first published in 1911. In this fifth edition the text has been thoroughly revised, and many chapters partially or completely rewritten. Major changes have been made in the subjects of malignant lesions of the nasopharynx, the pharynx and the larynx, simple neoplasms of the nasopharynx, treatment by sulfonamides, penicillin, radiotherapy and vitamins (combined to form a new chapter), allergy and nasal physiology, and laryngeal paralysis. Some rearrangement of the material has been made to provide a more logical text. This book, written by two British physicians, naturally reflects the British aspects of the subject. Likewise, the printing was done in Great Britain, and the sheets bound in the United States. The type, printing and illustrative work, including the color and radiographic plates, are excellent. The book should be in all medical libraries as a reference work and should prove valuable to all physicians interested in the subject.

A-B-C's of Sulfonamide and Antibiotic Therapy. By Perrin H. Long, M.D., F.R.C.P., professor of preventive medicine, Johns Hopkins University School of Medicine, and physician, Johns Hopkins Hospital. 12°, cloth, 231 pp. Philadelphia: W.B. Saunders Company, 1948. \$3.50.

This small manual represents the experience of the author in the use of the sulfonamides and antibiotics over a period of

twelve years. It is intended for the general practitioner and surgeon and should prove useful as a reference source in their daily practice. The volume is well published.

Plaster of Paris Technic. By Edwin O. Geckeler, M.D., professor of orthopedic surgery, and chief of the fracture service, Hahnemann Medical College and Hospital, Philadelphia. Second edition. 8°, cloth, 220 pp., 234 illustrations. Baltimore: Williams and Wilkins Company, 1948. \$3.00.

This second edition of a standard monograph, first published in 1944, has been revised, and many illustrations have been added. The book is mainly illustrative, with a small amount of text. It is recommended to orthopedists and to all persons using plaster and to medical libraries as a reference source.

Die Funktionelle Organisation Des Vegetativen Nervensystems. By W. R. Hess, o.ö. Professor der Physiologie an der Universität Zürich. 8°, cloth, 226 pp., with 80 illustrations and 1 table. Basel: Benno Schwabe and Company, 1948. 18.50 fr.

This well written monograph constitutes a comprehensive survey of present-day knowledge of the functions of the vegetative nervous system. There are nine chapters, beginning with peripheral autonomy and ending with dynamic principles. A comprehensive bibliography of eleven pages concludes the text. There is a good index. The book is well published in every way. It is recommended for all medical libraries and should be available to all neurologists.

A Textbook of General Physiology. By Philip H. Mitchell, Ph.D., Robert P. Brown, Professor of Biology, Brown University. Fourth edition. 8°, cloth, 927 pp., with 201 illustrations. New York: McGraw-Hill Book Company, Incorporated, 1948. \$7.50.

This standard college textbook, first published in 1923, has been thoroughly revised in this fourth edition. Extensive changes have been made in the chapters on excitation and contraction, the structure of living matter, permeability of cells and nutritive requirements. The chapter on biologic oxidation has been entirely rewritten, and a chapter on intermediary metabolism has been added. Lists of references are added to the various chapters, and a good index concludes the text. The book is well published and is recommended to all medical libraries as a reference source.

Bailey's Text-Book of Histology. Revised by Philip E. Smith, Ph.D., professor of anatomy, College of Physicians and Surgeons, Columbia University, and Wilfred M. Copenhaver, Ph.D., associate professor of anatomy, College of Physicians and Surgeons, Columbia University. Twelfth edition. 8°, cloth, 781 pp., with 455 illustrations. Baltimore: Williams and Wilkins Company, 1948. \$7.00.

This standard textbook, intended primarily for the use of first-year medical students, was first published in 1904 and since that time nineteen printings have been made, it was translated into Spanish in 1948. This twelfth edition has been revised throughout, and some extensive sections have been rewritten. Many new illustrations in color and half-tone have been included. Lists of selected references have been appended to the various chapters. There is a good index. The publishing is well done, and the volume is recommended to medical libraries as a reference source.

Management of Common Gastro-Intestinal Diseases. By Thomas A. Johnson. 8°, cloth, 280 pp., with 16 illustrations and 4 charts. Philadelphia: J. B. Lippincott Company, 1948. \$7.00.

This monograph in the *American Practitioners Series* is the joint work of twenty-two specialists in the field of gastroenterology. The authors, in short papers, epitomize the results of their experience in the treatment of a selected group of important gastrointestinal diseases. The book is written primarily for general practitioners and should prove of value to that class of physicians. The type and printing are excellent, but the use of a heavy filled shiny paper is uncalled for in a book of this type.

Edinburgh Post-Graduate Lectures in Medicine Volume IV 8°, cloth, 582 pp., with illustrations London Oliver and Boyd, 1948 18/- net.

This fourth volume of a standard series brings together in one place forty-one articles by different authors on subjects in the fields of medicine, surgery, pathology and therapeutics, already published in the *Edinburgh Medical Journal* during 1945-1947. An index has been supplied and the publishing, which is excellent in every way, is an outstanding example of good bookmaking. The series should be in all medical libraries.

Detailed Atlas of the Head and Neck By Raymond C. Truax, M.S., Ph.D., associate professor of anatomy, College of Physicians and Surgeons, Columbia University, and Carl E. Kellner, artist, Department of Anatomy, College of Physicians and Surgeons, Columbia University 4°, cloth, 162 pp., with 136 illustrations New York Oxford University Press, 1948 \$15.00

This beautiful atlas is the culmination of years of work by an anatomist and an artist. The color plates are excellent and compare favorably with foreign work of the same type. There is a comprehensive index to structures. The volume should be in all medical libraries and available to all surgeons who are interested in head surgery. The price is not expensive for this type of book.

Fatal and Rickettsial Infections of Man By Thomas Rivers, M.D., director of the hospital, The Rockefeller Institute for Medical Research 8°, cloth, 587 pp., with 77 illustrations, 6 plates Philadelphia J. B. Lippincott Company, 1948 \$5.00

This treatise is the joint work of twenty-seven authors. The early chapters discuss the general and special aspects of the subject. The remaining chapters consider the various viral and rickettsial diseases. The material is well arranged. Bibliographies are attached to the various chapters. There are large author and subject indexes. The type and printing are excellent, but the use of a heavily filled paper is not justified when all the color plates are inserts. The book is outstanding and should be in all medical libraries and available to all physicians and others interested in the subject.

Technique of Treatment for the Cerebral Palsy Child By Paula F. Egel, cerebral-palsy director, Children's Hospital, Buffalo, New York 8°, cloth, 203 pp., with illustrations St. Louis C. V. Mosby Company, 1948 \$3.50

Miss Egel has had extensive experience in treating various types of cerebral palsy in children in institutions and in the home according to the methods of Dr. Phelps. The techniques used are outlined in detail and should prove invaluable to persons called upon to treat these patients. Mr. Tanner, in an appendix, presents a plan for the organization of a cerebral-palsy department in a children's hospital.

The illustrations are excellent, and the outline drawings present in detail the exercises for conditioned motion. There is a good index. The monograph should prove invaluable to nurses and other persons having to deal with cases of palsy.

Liver Injury, Transactions of the Seventh Conference, January 15 and 16, 1948, New York, New York Edited by F. W. Hübner, M.D., 8°, paper, 95 pp., with illustrations New York Josiah Macy, Jr., Foundation, 1948 \$1.50

The subjects discussed at this conference included radioactive methionine, protein formation, portal hypertension, hepatic blood flow, plutonium, liver-cell regeneration, hepatic excretory functions and serum lipids in liver disease. The complete series of conferences is essential for medical libraries.

Studies from The Rockefeller Institute for Medical Research Reports, Volume 136 8°, paper, 607 pp., with illustrations New York Rockefeller Institute for Medical Research, 1948 \$2.00

This volume presents in collected form the results of investigations carried on by research workers of the Rockefeller Institute or under grants and originally published in scattered periodicals and other publications. The period covered is approximately the last half of 1947 and the first half of 1948.

Radioactive Indicators Their Application in Biochemistry, Animal Physiology, and Pathology By George Hevesy 8°, cloth, 556 pp., with illustrations New York Interscience Publishers Limited, 1948 \$10.00

This outstanding work in a new field presents a survey of work carried out with radioactive indicators in the subjects of animal physiology, pathology and biochemistry. The pertinent literature has been analyzed, and the references are appended to the text throughout the book. The material is well organized proceeding from the general to the special aspects of the subject. The type, paper and printing are excellent. The volume should be in all medical and all libraries and should be available to all persons interested in the subject. It should have a long life as an authoritative reference work.

A Treatise on Contemporary Religious Jurisprudence By I. H. Rubenstein, of the Illinois Bar 8°, cloth, 120 pp. Chicago Waldain Press, 1948 \$2.50

This monograph is devoted to a discussion of the civil, legal and criminal aspects of fortune telling, faith healing and pacifism. The part on faith healing appeared previously in the February 6, 1941 issue of *New England Journal of Medicine*. The text, which is profusely documented with citations from court records, is well written, and the material is well arranged in a typical legal style. An index would have made the volume more useful. Because of the documented section on faith healing the volume should be in the reference collections of all medical libraries.

The Mechanism of Abdominal Pain By V. J. Kinsella, M.B., Ch.B. (Svd.) F.R.C.S. (Eng.) 8°, cloth, 230 pp., with 17 illustrations Sydney Australasian Medical Publishing Company Limited, 1948 32/6

The author contends that the mechanisms of splanchnic pain do not differ essentially from those of somatic pain, and presents evidence to support his contention. He believes that true visceral pain and tenderness have an adequate anatomic basis and gives reasons for a belief in direct visceral tenderness. He stresses the fundamental inadequacy of experiments on pain in animals. The author postulates a neuro-humoral basis for abdominal pain to replace the neuronal theory, and considers that this simple conception replaces that of indirect mechanisms and makes the clinical examination of the abdomen more simple and exact. A list of references and an index conclude the text. The book is well published and should be available to all persons interested in the subject.

Treatise on Surgical Infections By Frank L. Meloney, M.D., associate professor of clinical surgery, College of Physicians and Surgeons, Columbia University, and associate visiting surgeon, Presbyterian Hospital, New York City 8°, cloth, 715 pp. New York Oxford University Press, 1948 \$12.00 Oxford Medical Publication

This book is the result of investigations carried on by the author and his associates during the past twenty years. It includes experience with the sulfonamides and the antibiotics. It is written especially for operating-room personnel, laboratory workers and surgeons. It emphasizes high standards of sterile technique in the operating room and the necessity of close co-operation of the laboratory and the surgical clinic. A number of chapters are devoted to the treatment of infections by surgery, chemotherapy, zinc peroxide, bacteriophage and penicillin. The material is well written. Lists of pertinent references are appended to the various chapters. A comprehensive index concludes the text. The book is well published. A good type is used, and the illustrations are excellent. The book is recommended for all medical libraries as a standard reference work and should be available to all surgeons and laboratory workers.

A Public Relations Workshop A manual of practical public relations techniques prepared for the guidance of the national membership of the American Nurses' Association 8°, cloth, 32 pp., with 34 illustrations New York American Nurses' Association, Incorporated, 1948 \$3.00

This manual was prepared by Edward L. Bernays, counsel on public relations, for the purpose of making available to

nursing organizations the modern technics of public relations in all fields of publicity, including the press, radio and television, movies, direct mail and public meetings. The type, printing and paper are good, but the oblong size of the volume is awkward and bothersome. The same data could have been presented to advantage in a regular octavo form. The material in the book could be valuable to other than nursing organizations.

Your Baby The Complete Baby Book for Mothers and Fathers By Gladys Denny Shultz and Lee Forrest Hill, M.D. 8°, cloth, 278 pp., with illustrations. New York: Doubleday and Company, Incorporated, 1948. \$3.50.

This de luxe volume is intended for parents, including fathers, and presents instructions and advice on how to care for babies from the time of their birth through their second year and for preschool children from two to six years of age. The preliminary chapters are devoted to various aspects of pregnancy. The concluding chapters discuss formulas and recipes and common ailments and accidents. The illustrations, photographic reproductions and line drawings are excellent and form an important part of the book. The volume should appeal to obstetricians and pediatricians, who might profitably refer it to their patients.

Polio and its Problems By Roland H. Berg. With a foreword by Basil O'Connor, president of the National Foundation for Infantile Paralysis, Inc. 8°, cloth, 174 pp., with 24 illustrations. Philadelphia: J. B. Lippincott Company, 1948. \$3.00.

Dr. Berg has written a popular history of epidemic poliomyelitis beginning with the widespread epidemic that swept over the northeastern section of the United States in 1916 down to the present time. He relates in simple language the progress that has been made in combating the disease during the past thirty-odd years. The text has been printed with a good, large type on a soft nonglare paper pleasing to the eye. There is a good index. The book is recommended for all public libraries and for all medical-history collections.

An Account of the Weather and Diseases of South Carolina By Lionel Chalmers, M.D., of Charles-Town, South Carolina. In two volumes. Volume I. 8°, paper, portrait, 58 pp. London 1776. Selections reprinted, Charleston: South Carolina Medical Association, 1948. Free.

The Committee on Historical Medicine of the South Carolina Medical Association, in commemoration of the centennial of the Association occurring in 1948, issued this facsimile reproduction of an important early American imprint specially pertinent to the medical history of South Carolina. The original publication is very scarce, and the opportunity to obtain this excellent reproduction should be taken advantage of by all medical libraries and medical historians.

Hospital Trends and Development, 1940-1946 Edited by Arthur C. Bachmeyer, M.D., director, University of Chicago Clinics and director, hospital administration course, University of Chicago and Gerhard Hartman, Ph.D., superintendent, State University of Iowa. 8°, cloth, 819 pp., with illustrations. New York: Commonwealth Fund, 1948. \$5.50.

This composite volume covering the whole field of hospital administration and service comprises a large number of selected articles condensed from their original form in many periodicals published during the past few years. The makeup is excellent, but the lack of an index detracts from its reference value. The book is recommended for all medical, public-health and hospital libraries and to all hospital administrators.

The Alcoholic Woman. Case Studies in the Psychodynamics of Alcoholism By Benjamin Karpman, M.D., chief psychotherapist, St. Elizabeths Hospital, Washington, D.C. 8°, cloth, 241 pp., 3 diagrams. Washington: Linacre Press, 1948. \$3.75.

This monograph presents three extensive case histories of alcoholic women who had one factor in common: an unsatisfactory childhood environment characterized by parental stupidity or incompetence. In all 3 cases the acquaintance with alcohol was incidental and gradual, and gave no

hint that it would become a possessive force in their lives. The patients were treated with the method of "objective psychotherapy." This monograph should prove of value to psychiatrists and psychoanalysts.

The Clinical Application of Psychological Tests. Diagnostic Summaries and Case Studies By Roy Schafer, M.A., staff psychologist, Austen Riggs Foundation. Foreword by David Rapaport, Ph.D., Menninger Foundation. 8°, cloth, 346 pp. New York: International Universities Press, Incorporated, 1948. \$6.75.

This monograph presents a method of applying a battery of six clinical psychologic intelligence and personality tests to a series of appropriate cases. Two of the chapters are devoted to case studies of psychopathic disorders. The book is a sequel to the two-volume treatise by Rapaport, Gill and Schafer, entitled *Diagnostic Psychological Testing* (Chicago, 1945). The volume should be in all psychiatric and psychologic collections.

A Method of Anatomy. Descriptive and Deductive By J. C. Boileau Grant, M.C., M.B., Ch.B., F.R.C.S. (Edin.), professor of anatomy in the University of Toronto. Fourth edition. 4°, cloth, 852 pp., with 800 illustrations. Baltimore: Williams and Wilkins Company, 1948. \$7.00.

This fourth edition of a standard textbook has been thoroughly revised, and many parts of the text have been rewritten. First published in 1937 there have been thirteen printings to date, which speaks well for its popularity. The illustrations have been revised by addition and deletion, the total being brought to 800 for this edition. The type, printing and diagrammatic drawings are excellent. The book is recommended for all medical libraries as a standard reference source and should prove valuable to all persons interested in anatomy.

BOOK REVIEW

The Ciba Collection of Medical Illustrations. A compilation of pathological and anatomical paintings Prepared by Frank H. Netter, M.D. F°, cloth, 222 pp., with 191 full color plates. Summit, New Jersey: Ciba Pharmaceutical Products, Incorporated, 1948. \$6.50.

During the past eight years the Ciba company has published from time to time a series of educational illustrations, dealing with anatomy and pathology, which have been distributed to the medical profession as loose sheets in folders as published. The complete series is now brought together in one volume for the convenience of the many physicians who expressed a desire for such a publication. In reply to a letter issued by the company concerning the volume, 36,000 replies were received in the affirmative.

The material has been divided into four major sections as follows: lungs and chest, gastrointestinal tract, male reproductive organs and male and female mammary glands, and heart and aorta. The large color plates are accompanied on the same page by explanatory text. The artist, Dr. Netter, has long been engaged in medical illustrative work. His early illustrations were done in pure water color, but lately he has used casein paint, egg tempera and poster color in conjunction with the water color. Likewise, he has often employed colored pencils or pastels for shading over the painting or for working in fine detail.

In the illustrations in this book it has been the aim to stress clarity and simplification of detail. In the anatomic plates a schematic treatment has been adopted in the interest of detail. Likewise, color has been arbitrarily used to give emphasis and clarity. The arteries have been illustrated in bright red, and the veins in strong blue.

In the pathological illustrations, emphasis is placed on accurate color and realistic representation, and there is considerable simplification by the elimination of extraneous tissues, which obscures the essential pathologic condition.

The text is preceded by a table of contents listing each individual plate, and concluded with an index of subjects. The color work, both gross and minute, is excellent. The volume is an outstanding example of good bookmaking. It may be obtained only from the company.

(Notices on page xviii)

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THE METABOLISM OF THE RADIOACTIVE ELEMENTS CREATED BY NUCLEAR FISSION*

JOSEPH G. HAMILTON, M.D.†

BERKELEY AND SAN FRANCISCO, CALIFORNIA

THE appearance of new agents that carry with them a potential menace to the health and security of the public is bound to be accompanied by a very understandable attitude of fear. The highly dramatic introduction to the world at large of the release of atomic energy has produced an unprecedented degree of concern for public safety. Frequently, the concern expressed has assumed the proportion of panic owing to the lack of sufficient basic information on the part of those presenting their evaluations of the problems posed by this twentieth-century version of Pandora's box.

For example, considerable apprehension has been displayed concerning the disastrous effects that might follow the contamination of an inhabited area as the result of an underwater or subsurface explosion of an atomic bomb, which of course would release very large quantities of the radioactive fission products. There is no question that this type of action would serve to contaminate a considerable area to a dangerous degree. However, it is highly important that the inhabitants in the immediate vicinity realize that they are not all going to acquire the atomic-age version of the fate of the radium-dial painters; moreover, it is appropriate that steps be taken to keep to a minimum the incidence of radioactive poisoning after such an episode. Should such a problem ever arise, information and instruments are in hand to approach it intelligently and with a gratifying degree of effectiveness.

The work described in this article is but a small part of the many phases of the medical research activities within the atomic-energy program,‡ which were initiated during the war by the Manhattan Project and are now being continued by the Atomic Energy Commission. Space does not permit even

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†From the Crocker Laboratory and Division of Medical Physics (Berkeley) the Divisions of Medicine and Radiology (San Francisco) University of California.

‡Associate professor of medical physics, University of California Medical School (Berkeley); associate professor of experimental medicine and radiology, University of California Medical School (San Francisco).

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a partial enumeration of the many fields of investigation that are relevant to the medical aspects of the release of nuclear energy. It is important to indicate that these manifold activities are continuously accumulating the knowledge necessary to ensure the protection of the nation against the hazards inherent in the widespread development and applications of atomic energy. It is pertinent to recall that throughout the entire wartime period of activity of the Plutonium Project, there was not a single known episode of manifest radiation injury to the thousands of persons who worked on this program. The extent of scientific information, the number of trained and experienced personnel, and the availability of instruments for the detection of radioactivity is at a far higher level than is commonly supposed. Thus, the necessary safeguards for the peacetime applications of atomic energy are keeping pace with the rapid progress of this new field. At the same time the security of the nation has been strengthened against the possible consequences of military action in the event of an international disaster.

The phenomenon of nuclear fission in both the controlled release of atomic energy in the chain-reacting uranium pile and the instantaneous detonation of an atomic bomb is associated with the immediate emission of very energetic and penetrating neutrons and gamma rays. If an appreciable quantity of the fissionable element, such as uranium or plutonium, undergoes fission, a radioactive residue is left. This is due to the fact that the two atomic nuclei produced by the cleavage of a uranium or plutonium nucleus are unstable and thus radioactive. For this reason the radiation from either a chain-reacting pile or an atomic bomb continues after fission has ceased. These radioactive fragments from the fission of uranium and plutonium are called fission products and include radioactive isotopes of 34 different elements extending from zinc to the rare earth europium.¹ The explanation for the large number of different elements produced by fission is that the fissioning nucleus does

not divide into two equal parts but rather splits into nuclei of varying sizes. The fissionable element employed in the present chain-reacting piles is uranium, and coincidental to the formation of the fission products is the production of neptunium, which is the radioactive parent of plutonium.² Thus, the menace of radiation from the release of nuclear energy is not limited to the duration of the fission reaction but continues on afterward. The relative intensity of radioactivity arising from nuclear fission decreases with time, owing to the fact that the fission products are composed of a mixture of a large number of radioactive isotopes whose half lives range from a fraction of a second to almost a million years. The mixture of fission products emits both beta rays and penetrating gamma rays. The quantities of these radioactive substances that are created are enormous. The large chain-reacting piles at Hanford are operated to produce plutonium. This requires that after an appropriate interval the uranium in the pile be removed and plutonium isolated from the uranium and accompanying fission products by a very elaborate and complicated series of chemical processes. These piles produce plutonium in kilogram quantities, and at the same time a comparable mass of fission products is created. The quantity of radioactivity of the fission products with moderately long half lives falls in the range of hundred of millions of curies. The magnitude and potential dangers associated with this program become apparent when one makes a comparison to the history of the radium industry. Up to the time of World War II there had been isolated about 1 kilogram of radium, which possesses by definition 1000 curies of radioactivity. A large number of cases of radium poisoning had been reported, notably in the luminous-dial industry, a considerable proportion of which terminated fatally.

Radioactive substances can produce injury either by external or by internal radiation of the body. Of the two, the potentialities for injury are greater if the radioactive substance is within the body. The history of the circumstances surrounding the radium industry is illustrative of the point, for it appears fairly certain that the preponderance of fatal injuries arose from internal irradiation rather than external exposure. The medical program of the Plutonium Project, which was created during the war years under the direction of Dr. R. S. Stone, was faced with the responsibility of protecting the personnel against quantities of radioactivity that were of the order of a millionfold greater than had been encountered by the radium industry over a period of half a century. Here the problem had to be met quickly in the haste of wartime urgency for the thousands of scientists and technicians working on the Atomic Energy Project. One of the many research programs that arose from these needs was a survey of the metabolism of the various ele-

ments created by the release of nuclear energy. A summary of a portion of this work is presented here, and more detailed accounts of these and related studies have been published elsewhere.^{3, 4}

It is appropriate to mention a few of the salient factors involved in the problem of radioactive poisoning, for it was these considerations that shaped the pattern of the research to be described. To evaluate a potential hazard of a given radioactive element, it is necessary to consider the half life, radiation characteristics, route of entry into the body, assimilation, distribution, retention, excretion and relative susceptibility of the different organs or tissues to the radiations emitted by the deposited material. Radiation injury, both acute and chronic, is a function of the intensity of the irradiation and the duration of the exposure to the irradiation. A radioactive substance, either as an element or as a compound, may enter the body by one or more of four routes—namely, the lungs, the digestive tract, through cuts or abrasions, and the intact skin. Once the material has been absorbed, regardless of the portal of entry, it will be distributed to the many tissues of the body, where it will be taken up in widely varying concentrations and be retained for different intervals. The degree of injury will vary with the character of the radiation and the radiosensitivity of the irradiated organ or tissue. For example, alpha particles are relatively more destructive to most living tissue than beta or gamma rays, when the biologic effects are compared on the basis of equivalent amounts of total ionization in the tissue. Concerning variations in vulnerability to radiation, the bone marrow, which is the center of hemopoiesis, is very sensitive, whereas structures such as liver, brain and muscle are relatively radioresistant.

If the assimilation, distribution, retention and excretion of a given radioelement are determined, it is possible to make an estimate of the amount of exposure to such a substance that might be expected to produce either acute or chronic injury. If the tracer or metabolic studies are done in animal experiments, as in the investigations described below, a variable is introduced by the extrapolation of such results from the animals to man. However, in most instances this error is probably not significantly greater than individual variations between different human beings in their response to a novel biologic experience such as is offered to the body by most of the radioelements associated with the release of nuclear energy.

The available information was very limited at the time of the inception of the Plutonium Project concerning the metabolic properties of the elements whose radioactive isotopes arise from fission. Among the 34 different fission-product elements there are 14 whose radioactive isotopes possess half lives ranging from days to years and are produced in relatively high abundance by the fission process.

Almost all the total radioactivity arising from the fission-product mixture after it has decayed for a week is contained in the radioactive isotopes of these 14 elements, which are listed in Table 1. These elements possess metabolic patterns that differ not only from radium but also, in most instances, from one another. Prior to 1942, only one of this group, radioiodine, had received sufficient attention regarding its metabolic properties to permit a reasonable evaluation of the amount that could be tolerated in the body without producing manifest injury.⁷ A second fission product,

namely, the passage through the intact skin — was not investigated. The absorption, distribution, retention and excretion were investigated with each substance for the three channels of administration. Extensive radioautographic studies were made of organs in which a high degree of selective localization and retention took place, that a correlation might be established between the accumulation of the radioelement and the microscopical anatomy of the tissue.

The animals were killed at regular intervals after administration of each radioelement. Twelve to

TABLE 1 *Summary of the Metabolism of the Principal Members of the Long-Lived Fission Products and Neptunium and Plutonium in the Rat after Parenteral and Oral Administration*

RADIOELEMENT	HALF LIFE	FISSION YIELD %	ORAL ABSORPTION %	ACCUMULATION IN PRINCIPAL ORGAN OF RETENTION %	RATE OF ELIMINATION FROM PRINCIPAL ORGANS OF RETENTION
Strontium					
Sr ⁹⁰	53.0 days	4.6	5-60	70 (bone)	>200 days (bone)
Sr ⁹¹	25.0 yr				
Barium					
Ba ¹⁴⁰	12.8 days	6.1	5-60	60 (bone)	>50 days (bone)
Iodine					
I ¹³¹	8.0 days	2.8	100	20 (thyroid gland*)	>50 days (thyroid gland*)
Cesium					
Cs ¹³⁷	33.0 yr	—	100	45 (muscle)	15 days (muscle)
Yttrium					
Y ⁹⁰	57.0 days	5.9	< 0.05	65 (bone)	>500 days (bone)
Lanthanum					
La ¹⁴⁰	40.0 hr	6.1	< 0.05	70 (liver)	10 days (liver)
Cerium					
Ce ¹⁴⁴	28.0 days	5.7	< 0.05	30 (bone)	>25 days (bone)
Ce ¹⁴⁴	275.0 days	5.5	0.05	50 (liver)	10 days (liver)
Praseodymium					
Pr ¹⁴⁴	13.8 days	5.4	< 0.5	25 (bone)	100 days (bone)
Element 61					
61 ¹⁴⁴	3.7 yr	2.6	< 0.05	35 (liver)	>100 days (bone)
Zirconium					
Zr ⁹⁵	65.0 days	6.4	< 0.05	55 (bone)	>100 days (bone)
Columbium					
Cb ⁹⁵	37.0 days	6.4	< 0.5	50 (bone)	30 days (bone)
Ruthenium					
Ru ¹⁰⁶	42.0 days	3.7	< 0.05	25 (blood)	1 day (blood)
Ru ¹⁰⁶	1.0 yr	0.5			
Tellurium					
Te ¹³²	90.0 days	0.033	25.0	35 (kidneys)	20 days (kidneys)
Te ¹³²	32.0 days	0.19	25.0	15 (blood)	15 days (blood)
Xenon					
Xe ¹³⁵	5.3 days	4.5	Distribution proportional to fat content of body		
Neptunium					
Np ²³⁷	2.2 days	—	< 0.05	65 (bone)	half time in body 2 hr
Plutonium					
Pu ²³⁹	2.2 x 10 ⁴ yr	—	0.007	75 (bone)	>50 days (bone)
					>2 yr (bone)

*Human studies.⁷

radiostrontium, had been subjected to some investigation before this time but not in enough detail to satisfy the requirements of the medical research program of the Plutonium Project.^{8,9} The remaining 12 fission products and strontium, as well as neptunium and plutonium, were subjected to tracer studies so that their potential capacity to produce injury as internal radioactive poisons to those exposed to these substances could be predicted.

These tracer studies included a survey of the metabolism of the fission products in the carrier-free state,* and neptunium and plutonium in the rat after oral ingestion, inhalation and parenteral injection. The fourth possible route of entry —

*The term carrier free signifies that the radioelement was not diluted with measurable quantities of the stable nonradioactive form of the same element.

fifteen organs and tissues were removed, and their radioactivity determined, as well as the fraction eliminated in the excreta. The usual intervals before the animals were killed after receiving the radioactive materials were one, four, sixteen and sixty-four days. In a number of instances the experiments were extended to intervals of one hundred and twenty-eight and two hundred and fifty-six days. In several of the studies it was necessary to conclude the experiments prior to the sixty-four-day interval owing to the relatively short half lives of several of the radioisotopes employed.

The most significant metabolic characteristics of the fission products, and of neptunium and plutonium, are listed in Table 1. It will be noted that 8 of the fission products, as well as neptunium and plutonium, are not absorbed to any significant

degree by way of the digestive tract. After parenteral administration over half the fission-product group, as well as neptunium and plutonium, are accumulated by the skeleton and eliminated from this organ very slowly. The 5 members of the listed fission products that are absorbed from the digestive tract are strontium, barium, tellurium, iodine and cesium. Xenon is readily and rapidly absorbed from the lungs after inhalation and is as readily eliminated from the lungs. Strontium and barium are deposited and retained to a high degree

ton as shown in Figure 1. In lanthanum, cerium, praseodymium and element 61, there is an initially high degree of accumulation by the liver, but they are quite rapidly excreted from this organ, presumably by way of the bile. It will be noted from Table 1 that with the exception of columbium⁹⁵, and possibly strontium⁹⁰, cerium¹⁴⁴ and 61¹⁴⁷ the rates of elimination of the different fission products accumulated in the skeleton are less than their rates of radioactive decay. The fission products that fall into this category include strontium⁸⁹, yttrium⁹¹, zirconium⁹⁵, barium¹⁴⁰, lanthanum¹⁴⁰, cerium¹⁴¹ and praseodymium¹⁴³. With the exception of iodine in the thyroid gland, the remainder of the fission products listed in Table 1—namely, ruthenium¹⁰³, ruthenium¹⁰⁶, tellurium¹²⁷, tellurium¹²⁹, xenon¹³³ and cesium¹³⁵—are rapidly excreted and at rates considerably greater than their half lives.

The rates of elimination from the skeleton of neptunium and plutonium are quite slow. The daily excretion of plutonium in the rat falls to 0.01 per cent of the amount remaining in the body a year after the intramuscular administration of this radioactive element. Since neptunium²³⁵, which is the principal radioisotope of this element produced in the chain-reacting pile, has a half life of only two days, it is not possible to observe its rate of excretion after an extended interval. However, it is obvious that its rate of elimination from the skeleton is far less than its rate of radioactive decay.

Radioautographic studies were made of the distribution of the radioactive isotopes of strontium, zirconium, columbium, cerium, element 61 and plutonium in 5-micron sections of undecalcified rat femurs.^{3 10 11} The metabolism of strontium in the skeleton is very similar to that of calcium and, as might be expected, the radioautographs revealed that the accumulated radiostrontium in the femur was fairly evenly distributed throughout the mineral structure of the bone in young rats (Fig 2). It is assumed that the same results would be observed with barium, which possesses very similar chemical properties to those of strontium and whose metabolic characteristics are indistinguishable from those of strontium under the experimental conditions of these studies. The other radioelements studied by this technic revealed a startling deviation from the pattern of distribution observed with radiostrontium. Plutonium exhibits this phenomenon to a marked degree, and from Figure 3 it may be seen that most of this element is apparently deposited in the periosteum and endosteum, and in the region of the trabecular bone. These results suggest that plutonium in the trabecular structure is not incorporated within the mineral structure of the bone but rather is deposited in the covering of the trabeculae. The pattern of distribution in the

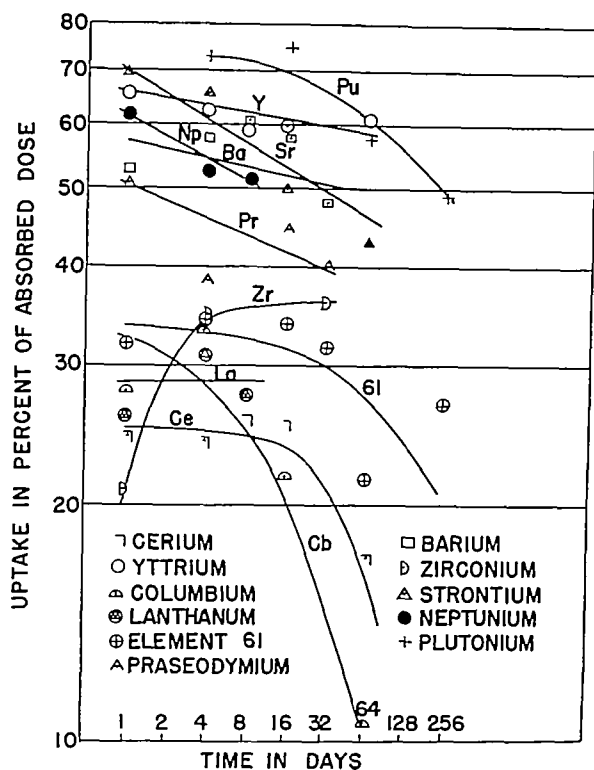


FIGURE 1 Deposition of Carrier-Free Fission Products and Neptunium and Plutonium in the Skeleton of the Rat after Parenteral Administration

by the skeleton. Iodine is accumulated and retained by the thyroid gland. Tellurium exhibits some deposition in the kidneys and blood, with a rapid rate of release from these organs. Cesium is distributed quite uniformly throughout all the tissues, the greatest accumulation occurring in the muscle, and is quite promptly excreted. The patterns of distribution of strontium, barium, tellurium, iodine and cesium in the body after oral and pulmonary absorption are indistinguishable from their metabolism after parenteral administration. With the exception of ruthenium, the remainder of the listed fission-product series, as well as neptunium and plutonium, show a considerable accumulation and varying degrees of retention by the skele-

bone of zirconium, columbium, cerium and element 61, as studied by this technic, resembles quite closely in most regards that observed with plutonium. A spotty distribution of cerium and element 61 has been observed within the cortical bone, which is believed to represent accumulation in the region of the small blood vessels. A similar effect is predicted for lanthanum and praseodymium in view of their closely related chemical and metabolic properties. A representative example of this pattern is shown for element 61 in Figure 4. The results obtained by the radioautographic studies suggest that the accumulation of these elements in the skeleton occurs in the superficial layers of the bone structure, and very possibly they are combined with proteins rather than being directly incorporated into the inorganic bone

significantly with time in the adult rat. Radioautographs from adult female rats that had received plutonium nearly a year before they were killed showed no significant differences in distribution in the bone when compared to bone radioautographs



FIGURE 2 Section of the Undecalcified Femur (Upper Photograph) and Corresponding Radioautograph (Lower) from a Young Rat that Had Received Radiostrontium One Week Before Death. Note the even deposition of radiostrontium throughout the mineralized structure of the shaft and the calcifying trabeculae beneath the epiphyseal plate (silver nitrate, hematoxylin and eosin stain $\times 3$).

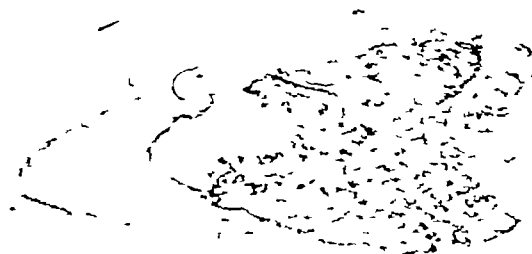


FIGURE 3 Section of the Undecalcified Femur (Upper Photograph) and the Corresponding Radioautograph (Lower) from an Adult Rat That Had Received Plutonium One Week before Death.

Note the superficial deposition of plutonium on the surfaces of the shaft and trabeculae, and the absence of plutonium from epiphyseal cartilage (silver nitrate, hematoxylin and eosin stain $\times 5$).

from animals killed a few days after the administration of this radioelement.

The direct introduction into the lungs of soluble compounds of the carrier-free fission products, and neptunium and plutonium, demonstrated that the radioelements that were not absorbed from the digestive tract were retained by the lungs to a considerable degree for a prolonged interval.⁴ Fission products exhibiting these characteristics included yttrium, zirconium, columbium, ruthenium, lanthanum, cerium and praseodymium. Although these pulmonary studies were not conducted with element 61, it is assumed that its behavior would be comparable in view of its other metabolic properties, which are closely akin to the group of substances named above. The same phenomenon was

salts as is apparently the case with strontium and presumably barium. It is noteworthy that the distribution pattern for this group of elements, which are laid down so differently in the skeleton from strontium, apparently does not appear to change

observed with neptunium and plutonium. Radioautographs demonstrated that the deposited radioactive materials were distributed throughout the lungs, including structures below the ductus alveolaris. No accumulation in the bronchial tree, lymph

free fission products.^{12, 13} The inhalation of these different radioactive aerosols was followed by the initial retention of approximately 75 per cent of each material. The retention was almost equally divided between the lungs and the upper respiratory tract (Fig 5). The material in the upper respiratory tract was rapidly removed, presumably by ciliary action, and appeared in the feces, and the fraction remaining in the lungs was eliminated quite slowly. Eight months after exposure to a plutonium oxide aerosol, which is an insoluble compound of the element, 4 per cent of the total quantity inhaled still remained in the lungs. Comparable values were observed with plutonyl nitrate, a soluble compound of the element, and with the long-lived fission-product mixture. There was very little absorption from the lungs, and subsequent

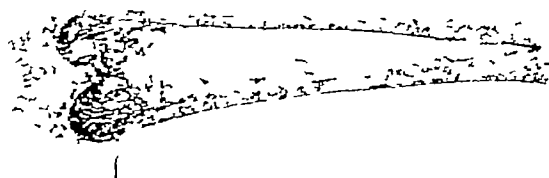
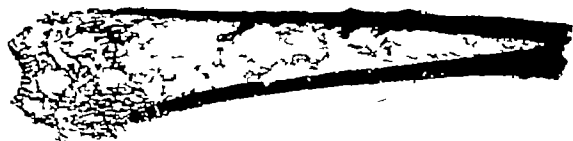


FIGURE 4 Section of the Undecalcified Femur (Upper Photograph) and Corresponding Radioautograph (Lower) from an Adult Rat that Had Received Element 61 Four Days before Death.

Note the superficial deposition of this radioactive element on the surfaces of the shaft and trabeculae. The spotty areas of accumulation within the shaft are believed to be depositions of element 61 in the immediate vicinity of the small blood vessels in the cortical bone (silver nitrate, hematoxylin and eosin stain $\times 3\frac{1}{2}$).



FIGURE 5 Section of the Lung (Upper Photograph) and Corresponding Radioautograph (Lower) from a Rat Killed Immediately after the Inhalation of a Plutonium Oxide Aerosol. Note the deposition of plutonium on the walls of the bronchi and throughout the alveolar structure (hematoxylin and eosin stain $\times 4$).

nodes or blood vessels was noted even after several months. Some absorption took place through the lungs for all the substances retained by this organ, and, except for ruthenium, most of the absorbed material was deposited in the skeleton, as would be expected from the parenteral metabolic studies. Fission products that are absorbed through the digestive tract — notably, strontium, barium, tellurium, iodine and cesium — were found to be quite readily absorbed through the lungs.

These experiments, which were quite qualitative in character, were later supplemented by a large series of aerosol studies using several different compounds of plutonium and a mixture of carrier-

deposition in the skeleton, after inhalation of the plutonium oxide and fission-product aerosols in an insoluble form. However, nearly 10 per cent of the plutonium, when inhaled as an aerosol of the soluble plutonyl nitrate, was absorbed through the

lungs in the first twenty-four hours and deposited in the skeleton. From the qualitative data obtained from tracheal-intubation studies using soluble compounds of the individual fission products, and the plutonyl nitrate aerosol experiments, it appears probable that the inhalation of aerosols of soluble compounds of all fission products, and neptunium, would result in a significant degree of absorption from the lungs.

Radioautographs of pulmonary tissue from the aerosol studies revealed that, immediately after inhalation, the active material was deposited in both the bronchial tree and the structures below the respiratory bronchioles. Within a day the material in the bronchial tree had vanished (Fig. 6). Presumably, it was moved out by ciliary action and swallowed with the sputum. The large fraction remaining in the lungs was quite evenly distributed throughout the alveoli, and the pattern of distribution showed little change with time for intervals extending to two hundred and fifty-six days after the initial exposure. The slow and continued release of active material from the alveoli probably also took place primarily by way of the bronchial tree. This deduction is based on the observation that the fecal excretion of plutonium and the fission-product mixture closely corresponds to the elimination of these materials from the lungs.

The outstanding characteristic of 9 of the fission products described in this report, as well as neptunium and plutonium, to be accumulated and tenaciously retained by the skeleton has a most ominous significance. Justification for this opinion is borne out by the tragic situation that has surrounded the radium industry. There is evidence that the prolonged retention of 1 microgm of radium may result in the appearance of bone tumors with a fatal outcome. Somewhat larger quantities of radium, in the range of 10 microgm deposited in the skeleton, are frequently associated with aplastic anemia and occasionally leukemia. These conditions are presumably the result of the prolonged bombardment of the very radiosensitive bone marrow and the bone itself by the radiations arising from the radium deposited within the skeleton. The gloomy picture of radium poisoning is darkened further by the fact that, to date, no successful method has been developed for removing significant quantities of radium from the body once it has been locked in the mineral structure of the bone.

The fission products that localize in the skeleton are similar to radium in that they also tend to be tenaciously held in that organ, and, to date, no satisfactory procedure for removing these substances from the bone has been developed.^{14, 15} A number of considerations reduce the relative menace of these fission products and neptunium¹⁹ as radioactive poisons in comparison to radium. In the first place they give up much less energy per dis-

integration, and the density of ionization is relatively much less since they emit only beta and gamma rays. Moreover, on the basis of an equal amount of ionization per unit volume of tissue, alpha particles are biologically considerably more destructive than beta and gamma irradiation. Secondly, with the exception of strontium⁹⁰ and ⁶¹La¹⁴⁷ the more abundant fission products that are accumulated in the skeleton possess half lives of less than a year, whereas the half life of radium is



FIGURE 6 Section of the Lung (Upper Photograph) and Corresponding Radioautograph (Lower) from a Rat Killed One Day after Inhalation of an Aerosol of Plutonium Oxide

The plutonium has disappeared from the bronchial surfaces, but it is widely distributed throughout the alveolar structures (hematoxylin and eosin stain $\times 4$)

approximately sixteen hundred years. Most of these fission products have half lives in the range of two weeks to two months. Thirdly, with the exception of strontium and barium, a negligible degree of absorption of these fission products and neptunium takes place through the digestive tract. However, with this group of radioelements there is one consideration that tends in part to counterbalance the considerations listed above, and that is the property possessed by a number of them to concentrate themselves in the immediate vicinity

of the bone marrow as contrasted to the more diffuse distribution of radium throughout the mineral structure of the skeleton. This behavior tends to enhance their radiotoxicity on the basis of both geometrical considerations and a minimal amount of self-absorption of the beta radiations, which are quite soft for several of the fission products under discussion. Plutonium shares the dangerous characteristics of radium—namely, a long half life (22,400 years), the emission of alpha particles, and the selective deposition and prolonged retention by the skeleton. In addition, the property of accumulating in the regions immediately adjacent to the bone marrow gives plutonium a significantly greater degree of radiotoxicity than an equivalent amount of radium. The only two metabolic properties of plutonium that tend to reduce this hazardous quality are the facts that it is absorbed to a negligible degree from the digestive tract and, presumably, that it is absorbed much less readily from the lungs than radium. Extensive studies have been made in an attempt to develop procedures that might effect the release of plutonium deposited in the bone. To date, practical progress in this direction has been discouraging.^{14 15}

In conclusion it should be said that there is no new major mystery surrounding the problem of protection against the radioactive products associated with the release of atomic energy. The physical phenomenon of radioactivity and its biologic actions have been known and subjected to intensive investigation for half a century. Recently, consideration has to be given to a much larger

quantity of radioactivity arising from a somewhat greater number of radioactive elements than those which normally occur in nature. Although some of the problems presented by this new situation are formidable, to say the least, in retrospect many other formidable problems have been successfully passed by those working in the medical and related biologic sciences.

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THE RADIATION SYNDROME*

ELIZABETH E. PAINTER, Ph.D.,† AND AUSTIN M. BRUES, M.D.‡

CHICAGO, ILLINOIS

IN EARLIER studies of radiation effects in mammals, dosages of 1000 r and above have generally been employed locally or over large areas of the body. Actually, when irradiation is given as a single total-body dosage, the quantity necessary to kill 50 per cent of the animals in thirty days or less is relatively small: 175 to 250 r for the guinea pig, 325 r for the dog, 350 r for the goat, 530 r for mice, 600 r for rats, and 800 r for rabbits.^{1,2} Where the LD₅₀ for man lies is questionable, but it is probably somewhere between those for the goat and the mouse.³

Since Hiroshima, various writers⁴⁻⁷ have reported the effects of very high instantaneous dosages of radiation. The fact that the victims of the atomic bombing showed a more complicated picture than the radiation syndrome alone is due not only to the blast effects but also to thermal effects that produced severe, superficial flash burns in a large proportion of the affected population. The ultraviolet light given off at the moment of detonation may also have been a factor.⁸ In other respects the persons exposed to radiation from the atomic bomb appear to have shown a clinical picture extraordinarily similar to that which has been seen in laboratory animals.

In the 1920's the work of Warren and Whipple⁹ and of Ivy et al.¹⁰ contributed much to knowledge of the gastrointestinal changes following radiation. Their work indicated that these changes may be responsible for the conditions leading to early death as well as changes of the blood-forming organs. Much of the literature on the effects of radiation upon the stomach and the intestines has been reviewed by Desjardins.¹¹ During this period studies on a variety of physiologic systems were presented by Swann.¹² Thorough blood studies were made on animals by Levin¹³ and on man by Lapatsanis.¹⁴

In the next decade the work of many investigators in the field of radiation centered on the measurement and standardization of dosage, on the question of "tolerance" and on the treatment of radiation sickness in man during and after x-ray therapy. Radiation sickness was compared with all types of shock and was treated in like manner. Much of the work was qualitative and not conclusive. Reviews by Pohle,¹⁵ by Steinberg¹⁶ and by Medinger and Craver¹⁷ are helpful in their coverage of the literature, but are somewhat discouraging so far

as the solution of the problem is concerned. For radiation therapy, they suggest dividing the doses or giving continuous radiation for a long time at a very low rate (0.8 to 0.9 r per hour) to prevent the occurrence of the initial phase of radiation sickness. It appears that of the drugs studied, sodium chloride, benzedrine (amphetamine), benadryl and epinephrine¹⁸⁻²⁰ are of some therapeutic value, whereas liver extract, components of the vitamin B complex and vitamin C, and pentose nucleotides are not clearly restorative. Vitamin C, pentose nucleotides and nicotinamide will lengthen the survival time for mice when they are given for several days prior to exposure to x-rays. They will have little or no effect on survival time when given after irradiation.⁶ Estrogenic hormones also appear to exert a protective effect when given several days before irradiation.²¹ Steinberg¹⁶ and others believe that further investigations should be made on the adrenal cortex and its possible alterations to throw light upon the development of more adequate therapeutic measures. Recently, Ellinger²² has attempted to establish a pharmacologic basis for use of substances in the treatment of radiation damage. He has found that the mortality in mice can be reduced by daily doses of desoxycorticosterone and that the fat index (accumulation of sudanophil fat) in mice can be reduced by daily doses of components of the vitamin B complex and vitamin C. The effectiveness of adrenocortical material has not been verified universally.²¹

Early in the 1940's Warren and his co-workers²³ presented a thorough review of the pathology associated with radiation damage of normal tissues. Later, Warren briefly reviewed some specific biologic changes following radiation. It is the purpose of this paper to summarize the theoretical aspects of the biologic action of ionizing rays upon the organism and to outline the clinical manifestations of the radiation syndrome. The references selected for the following discussion represent both a review of the literature and experimental data gathered during the past five years.

THEORETICAL ASPECTS

Crowther,²⁴ in an analysis of studies of other investigators using simple systems such as single cells and unicellular organisms, proposes that the biologic action of radiation is specific upon the nucleus, in that this structure in the resting stage is twenty-five times as sensitive as the cytoplasm of the cell. Two contrasting theories are proposed. The one that he calls the "poison" theory postulates

*From the Argonne National Laboratory.

†Assistant professor of physiology, University of Illinois College of Medicine.

‡Director, Biology Division, Argonne National Laboratory, associate professor of medicine, University of Chicago, the School of Medicine and Institute of Radiology and Biophysics.

that, by means of photochemical action on the substance of the nucleus, a certain amount of some unspecified poisonous material accumulates and diffuses to the outlying structures, which then manifest the changes observed. The second or "target" theory assumes the occurrence of a change wherever a pair of ions is produced within the sensitive structure and enables calculation of this "sensitive volume." Since genes are hit so readily, Crowther believes that the strong genetic effect is consistent with the discontinuous distribution of the x-ray energy being absorbed. He favors the second theory and is supported in his contention by Reboul²⁶ in his mathematical presentation of the biologic effects of radiation. The target theory is discussed in detail by Lea²⁷ as a likely explanation for gene mutations or chromosome breakage following the passage of an ionizing particle through such structures.

Zirkle²⁸ points out that the variations in relative biologic effectiveness of different types of radiation can be explained by differences in specific ionization of these rays in the tissue. To determine the specific ionization, the average ionization per unit length of alpha or beta tracks in the tissue must be calculated, the unit of expression being the number of ion pairs produced per centimeter of the ionizing track in tissue. This increases progressively from fast beta rays to gamma rays, and then to hard and soft x-rays, fast neutrons and alpha rays — that is, the alpha rays have the greatest specific ionization. By the term relative biologic effectiveness, Zirkle implies the use of some definite criteria for determining the effectiveness, such as gene mutations, inhibition of cell division and threshold erythema.

When comparisons of two or more types of ionizing radiations are made upon simple systems, viruses, bacteria, drosophila, chick fibroblasts and so forth, Zirkle finds that the biologic effectiveness decreases as the specific ionization increases. For more complicated systems, like the higher phyla of plants (seedlings of flowers and vegetables) and of animals (mouse, rabbit, pig and man), biologic effectiveness increases, in general, as the specific ionization increases.

Another hypothesis is that of Failla,²⁹ whose thesis is illustrated by the experimental work of Sugiura^{30, 31}. The latter was interested in the mechanism of the radiosensitivity of mouse sarcoma 180 cells and the part played by the host tissue in their "takes," since it has been generally assumed that the lethal dosage of x-rays for tumors growing in animals is much smaller than the dosage required to kill the same tumors *in vitro*. He found that there is a critical period for the host cells during the first two to forty-eight hours after radiation, at which time there is disorganization of these cells and, parallel with this, a decrease in the number of "takes" of tumor transplants. At six or seven days after radiation, however, the "takes" are 100 per

cent successful. Further experimentation indicated a relation between these differences and hydration phenomena — that is, the ions produced by the radiation give rise to chemical changes in the constituents of the host cells with an alteration in their normal state and subsequent increase in their osmotic pressure. Ionizing radiation, therefore, initiates the swelling of cells. The swelling coupled with other changes caused by the radiation leads to cell death. The relation of chemical changes produced by radiation to the above phenomena requires much further explanation.

That chemical changes occur in aqueous systems as a result of ionizing radiation is now well understood.³² The production of hydrogen peroxide and other oxidants in irradiated water is used by Barron³³ in explanation of the specific radiation sensitivity of certain enzymes (those having sulfhydryl groups) in contrast to the more radio-resistant enzymes, which at the same time are less sensitive to oxidative inactivation. Fricke's³⁴ work on the reduction of oxygen to hydrogen peroxide by irradiation of its aqueous solution was the introduction to this concept. The oxidation theory of chemical alteration is supported by workers whose investigations show that there is an increased resistance to the action of x-rays when the blood flow through an area being irradiated is reduced,³⁵ or when animals are partially dehydrated before exposure to radiation.²

In his recent book, Lea²⁷ summarizes all the possible modes of biologic action of radiations. His main thesis is that the biologic effects are due to chemical changes induced by radiation. The greater part of these changes is attributed to the direct action of radiation with production of ionization in particular molecules and the indirect action of ionized water inside and outside the cells. No doubt other molecular effects of radiation are concerned in radiation effects, but the changes in water are best understood and, because of the abundance of water in living matter, may be the most important.

THE RADIATION SYNDROME

The clinical sequence of the radiation syndrome is dependent upon several factors. Obviously, it can be clearly defined only through constant observation of the same animal. It is dependent upon whether the total dosage is given homogeneously to the whole body or whether it is confined to certain parts of the body. Localization may be accomplished by intense homogeneous radiation of part of the body or by exposure to soft radiation (alpha or beta rays) that may be directed toward external surfaces of the body or through deposition of radioactive isotopes having the tendency to localize in certain tissues or cells. Thus, partial body radiation may involve either a segment of the body or a particular group of tissues.

Radiation may be given by single, intermittent or continuous treatment, and the dosage rate may be varied. These factors will influence the syndrome considerably.¹⁶⁻¹⁷

Despite the complexity of the problem as indicated above, it is found that the general features of the clinical course are similar whether ionization in the tissue is produced by penetrating external radiation²⁰⁻²⁶⁻²⁸ or by alpha or beta emitters from internally deposited radioactive materials.²⁻²⁹ Slight variations in the clinical course are indicated by mortality waves and by coincidental clinical observations. It is interesting to note the correlation of the underlying changes occurring on a cellular level with such diverse forms of damage as beta-ray exposure to skin.⁴⁰ These separate and distinct time periods for gross pathophysiologic changes in skin were originally defined by Miescher⁴¹ as occurring on or at the end of the first day, the first week and the first month after irradiation. Telangiectasis occurs at about one year. The mechanisms involved in the production of these three erythemas and of the telangiectasis have been elaborated on by Pohle,⁴² Borak⁴³ and others.

If single supralethal dosages of total-body radiation are given to guinea pigs and mice, they will die under the beam with generalized cellular destruction.⁴⁴⁻⁴⁵ Dogs and rats will die in four to six days with severe dehydration.⁹⁻⁴⁶

At single total-body dosages equivalent to killing within thirty days of 50 per cent of the animals (325 r for dogs), the manifestations are somewhat different from those described above and are spaced over a sufficiently long period to allow for detailed physiologic studies. At such dosages, the gross clinical changes may be classified under four periods in the different species: initial shock or radiation sickness, beginning after a latent phase of one hour following the radiation and lasting sometimes as long as twenty-four hours, acute period lasting from nine to twenty-one days, subacute period lasting from thirty to two hundred days, and chronic period, from two hundred days on. Careful study of the syndrome will indicate additional phases within the above. Manifestations differ in various species, but the general pattern is seen in all.

Initial Shock (Radiation Sickness)

After an LD₅₀ of external radiation, there occurs a latent period of one to two hours in the different species, during which no significant physiologic changes are observed. The dog, rat, mouse, guinea pig, goat and man show signs of radiation sickness during the first six hours. This condition is characterized by prostration, diarrhea, urination, lacrimation and decreased food and water consumption. Some rabbits as well as chickens will die at three to forty-eight hours. In addition, rabbits show granulocytosis during the first twenty-four hours and a marked fall in blood pressure, approxi-

mately 50 to 60 per cent below the control levels one or two hours after irradiation. The change in pressure is due in part to autonomic factors as shown by partial protection with atropine or by vagotomy and in part to circulating factors as shown by transfusion experiments. Control studies on normal recipients from which half the blood volume had been removed and gradually replaced with the same quantity of blood from normal donors showed a 5-mm change in blood pressure, whereas normal recipients transfused in a similar manner with blood from irradiated donors showed a 26.5-mm drop in pressure. These circulatory changes are accompanied by leakage of plasma and its constituents from cutaneous vessels, observed as diffusion of the blue dye, T-1824, and of fluorescein.²⁰⁻⁴⁷

In man and in the dog, nausea, vomiting and anorexia occur during this early period, but there appears to be no significant change in blood pressure. For the most part, changes in blood chemistry in all species examined are slight.

The extent to which early treatment of radiation sickness alleviates or delays the clinical symptoms that occur at nine to twenty-one days (acute period) has not yet been determined.

Acute Period

This is the period when most of the animals given a thirty-day LD₅₀ of external radiation die. Generally, animals show recovery from the initial lethargic state a few hours after irradiation and remain in apparently good clinical condition until the seventh or eighth day. The depression that follows may be either gradual or abrupt and may occur at any time in the next few days. Before clinically visible changes appear, however, there are alterations in many physiologic systems. The most sensitive systems—that is, those showing the earliest changes with the lowest dosages of radiation—are the blood-forming organs, the gastrointestinal tract and the gonads. The absolute lymphocyte count declines abruptly, whereas the count of granulocytes declines more gradually (after the initial granulocytosis in rabbits). Diminution in number of circulating lymphocytes is the most sensitive evidence of exposure yet found. Evidence of the changes in other systems is manifested on the third or fourth day by increased sedimentation rate of the blood cells and prolonged clotting time. On the sixth to the tenth day, there is an increased plasma clearance of phenol red (with return to normal about the twelfth to the fourteenth day), an increase in the plasma volume as the red-cell volume decreases, rise in blood sugar, later followed by a fall, increase in plasma histamine, heparin, cholesterol and acetone bodies, diminution of plasma nonprotein nitrogen, urea nitrogen, "polypeptide nitrogen" and total proteins followed by a late increase, decrease in fecal and urinary coproporphyrins, elevated urobilinogen and bilirubin, lowering

of gastric acidity, reduced absorption of glucose by the intestine and delayed emptying of the intestine, and ulcers begin to appear in mouths of dogs.¹ The relation of these numerous findings to the underlying physiologic and structural changes and to compensatory processes is not in all cases clear.

The late (or terminal) changes occur precipitously three or four days before death, and some of them may appear briefly in survivors before a gradual recovery sets in. These include scattered petechiae and diffuse hemorrhages in the skin, a marked rise in heart rate, a gradual fall in blood pressure, an increase in body temperature and, in some animals, edema of the neck and mediastinal regions. The cardiovascular damage has been observed most frequently in the dog. Changes in the heart are indicated by the change in the electrocardiogram, which shows a slight increase in the PR interval, a low take-off and an inverted T wave in Leads 1 and 2. This has been most obvious in animals that, on autopsy, showed extensive hemorrhages in the cardiac muscle. Changes in the peripheral circulation are apparent in many ways: there is difficulty in drawing blood from small vessels, clumping of red cells with loss of plasma from vessels can be observed microscopically, and slight trauma to skin results in ecchymosis or edema. On autopsy, widespread hemorrhages and petechiae are found throughout all the tissues, including the central nervous system and the kidneys.

A highly significant factor in the bleeding tendency has been described by Allen and Jacobson,⁴⁸ who observed that a greatly increased heparin concentration ran parallel to the prolonged clotting

by direct and indirect metabolic measurements. At this stage the picture is typical of a general toxic reaction. Toxins may be expected in the presence of bacterial infections occurring with the extreme leukopenia and may also come from the products of tissue breakdown or of extravasated blood.

It may be of interest to mention threshold dosages of total-body x-ray that will just produce certain of the physiologic effects discussed above. These are approximately as shown in Table 1, according to Prosser.⁴⁹

Subacute Period

Animals surviving a single LD₅₀ of radiation for thirty days or longer fall into this category. Dogs receiving daily x-ray dosages of 25 r or below or low dosages of the internal emitters, plutonium or strontium⁵⁰ (radium in man⁵¹) will die between thirty and two hundred days.

The characteristic changes during this period are severe anemia, emaciation, loss of hair and pigmentation of the skin, terminally, ulcers are found in the duodenum and jejunum of dogs. The animals that receive the internal emitters or daily dosages of x-rays do not show the early shock-like symptoms, but they may show from two to four depression waves between the original injection, or the first exposure to radiation, and death. These waves are manifested by reduction in the red-cell count, by general lethargy and by decreased food and water intake. Hematologic changes develop very gradually and show fluctuations with the depression waves, as do the changes in other physiologic systems. Several days prior to death there occurs an increase in heart rate and an increase in body temperature similar to the changes observed in dogs in the terminal phase of the acute period.

Chronic Period

In animals receiving still lower dosages of x, alpha or gamma rays, decreased life-span, graying of dark-haired animals and the development of tumors constitute the chronic changes after irradiation. In mice, lymphomas, lymphatic leukemia and lung tumors are readily induced by total-body irradiation. Many species develop tumors of certain tissues after local irradiation by alpha-emitting or beta-emitting substances. Especially noteworthy are the multiple skin tumors resulting from external beta irradiation and bone tumors following absorption of radium, strontium⁵⁰, plutonium and other radioactive isotopes.⁵² In addition to high incidences of malignant tumors in areas receiving relatively heavy dosages of radiation, the normal tumor incidence in various species of animals is increased (or tumor development is accelerated) after either a single high dose or repeated or continuous exposure at a low level.⁵³ The degree of enhancement of the normal tumor incidence ap-

TABLE 1 *Effects of Threshold Dosages of Total-Body X-Rays*

DOSEAGE	EFFECT
r	
25	Lymphopenia (dogs, rabbits, rats)
50	Granulocytopenia (dogs)
	Reduction in platelet count (dogs)
	Reduction in blood pressure (rabbits)
	Elevation of basal metabolism (rats) ⁴⁸
	Inhibition of intestinal absorption of glucose (rats)
100	Granulocytopenia (rabbits)
	Elevation of sedimentation rate (dogs)
200	Anemia (dogs, rabbits)
	Absence of reticulocytes (dogs)
	Prolongation of clotting time (dogs)

time. The progressive hemorrhages were stopped and the clotting time was returned to normal by the administration of toluidine blue or protamine, both of which inactivate the heparin.

In this later period there is also evidence of liver dysfunction as shown by the changes in bile-pigment metabolism. Plasma nonprotein nitrogen and urea nitrogen show a marked rise, associated with the increase in body temperature, with the decreased kidney function and with an increase in total tissue breakdown. The latter has been determined

pears proportional to the amount of absorbed radiation, although its occurrence at low radiation levels (below 0.5 to 1 r daily) has not been clearly demonstrated, owing to the experimental difficulty of showing the low incidences that might be expected. Whether a threshold exists for carcinogenesis or effects on longevity is therefore unknown.

A noteworthy feature of the carcinogenic effect of radiations is the duration of the latent period, which, even under the most intense local stimulation, is rarely less than six months. It appears that radiation carcinogenesis is little dependent on species, in contrast to chemical carcinogenesis, in which the metabolism of the carcinogen may be a factor.

THERAPY

As mentioned above, adequate methods of treatment for radiation damage are lacking. The main objectives in the management of patients are to maintain adequate fluid and acid-base balance, to control infectious processes, to combat the hemorrhagic phenomena and to correct anemia and blood-volume changes.

Investigations have been most successful along the lines of increasing survival time, and of reducing the bleeding tendency. In the latter case, protamine and toluidine blue offer some promise. Penicillin and other antibiotics appear indicated for the control of infection. It appears, in general, that other forms of therapy are as yet not established (for example, adrenocortical material and rutin), must be given prior to irradiation or (as in several adjuvants mentioned above) apply only to the initial reaction as seen during the day following x-ray therapy.

DISCUSSION

No single clinical reaction is peculiarly specific for radiation damage. A similar preterminal course with leukopenia and high sensitivity of dividing cells is found with such agents as the nitrogen mustards⁵⁴ and urethane⁵⁵, the acute terminal course with fever and petechiae is characteristic of acute infections and of many diseases. There are striking similarities to anaphylactic shock and to the nonspecific (alarm) reactions to a variety of diverse toxic agents given in sublethal amounts,⁵⁶ and to the agranulocytic states accompanying drug sensitization. Many of the delayed effects of radiation can be duplicated by various toxic chemicals, such as anemia and leukemia in benzol poisoning, or tumor induction by hydrocarbons or ultraviolet light.

The relation between the initial physical and chemical effects of radiation remains largely to be worked out. It seems reasonable to believe that the primary effects all occur during radiation and for a brief period thereafter, since the lifetime of the chemical products of ionization in water is short.

With the exception of the initial reaction, the acute phenomenon of the radiation syndrome follows a latent period during which cell damage and atrophy of the more sensitive tissues occur. Since these tissues (blood-forming organs, intestine and gonads) are proliferative, it is tempting to suggest that damage to chromosomes (which is known to lead to cell death at a subsequent cell division) accounts for the damage. The picture may well be more complicated than this. In any case, many of the features of the radiation syndrome can be accounted for by destruction of the sensitive cell types. There is some evidence that agranulocytosis, rather than lymphopenia, correlates with the lethal dose among the various species of animals.⁵⁷ Many of the early changes in the syndrome, such as increased renal blood flow and elevated sedimentation rate, suggest the presence of circulating toxins, whereas many of the late changes appear to be associated with hemorrhage due to the release of heparinoid material into the blood, probably from injured cells.

The nature of toxic materials that may be involved in the shock-like state is far from clear. It will be recalled that in certain forms of traumatic shock in which such toxins are present, bacteria have been clearly shown to be responsible.⁵⁸

The events leading to the chronic phenomena are still less well understood. The fact that radiation induces genetic changes has suggested that carcinogenesis is due to similar changes in somatic cells resulting in mutant cells that have the characteristics of neoplasia, but various other explanations may be entertained. The shortening of life span has been loosely termed "increased aging," but evidence for this involves all too meager understanding of the aging process, and will await study of the various pathologic states that lead to shortening of life, among which tumor formation is probably only one.

SUMMARY

The radiation syndrome, produced by a single total-body thirty-day LD₅₀ of external radiation or of internal emitters of alpha or gamma rays, is characterized by three separate and distinct periods: the initial shock reaction or radiation sickness, the acute and the subacute. The initial shock may last from three to forty-eight hours. Occasionally rabbits and chickens die during the initial period. Other animals, such as dogs, rats, guinea pigs and goats, do not die, but show prostration, diarrhea, urination, lacrimation and decreased food and water consumption. In addition, man and the dog often vomit.

The acute period lasts from nine to twenty-one days, during which most of the animals die. The preterminal changes and the sharp delineation of the terminal signs are discussed in detail. Some of the radiation effects are directly due to destruc-

tion of certain tissue elements. Many others are indirect and may be attributed to infections, toxic agents, hypoxia and other secondary factors.

Animals surviving thirty days or more fall into the subacute category, where fluctuations of recovery and depression of the leukocytes do not permit the use of the white-cell count for determining the progressive changes of radiation damage. A severe anemia, emaciation and graying of dark-haired animals are the usual signs of the radiation syndrome in this phase. The chronic phase is characterized by shortening of life and sporadic increase in tumors.

Nearly every physiologic system shows damage after total-body irradiation. The effects are non-specific. Many of the same manifestations are shown in the animal organism by the administration of the nitrogen mustards or urethane, in anaphylactic shock, agranulocytosis, the "alarm reaction" of Selye and benzol poisoning. Damage to the radio-sensitive cells will explain a great part of the picture, but much further understanding of the syndrome is required in the interest of prevention and therapy.

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VARICOCELE*

Symptomatology and Surgical Concepts

RAYMOND O. OLSON, M.D.,† AND ERIC P. STONE, M.D.‡

FRAMINGHAM, MASSACHUSETTS

IN RECENT years the treatment of symptomatic varicocele has become a subject of renewed endeavor. The interest was stimulated by the degree of disability this condition caused among members of the armed forces during World War II. Low scrotal-vein ligation, the operation in vogue prior to 1942, had fallen into disrepute because of persistence of symptoms and the frequency of surgical complications. For these reasons a new operative technic, which had been popularized in Latin America, was tried by Army surgeons.^{1,2} Reported series of cases¹⁻⁴ in which this operation was performed and evaluated showed the procedure to be surprisingly effective.

In civilian life the discomfort and disability associated with varicocele continue to interfere with the efficiency of thousands of workers. In an attempt to relieve those who sought relief at this hospital, this newer technic of high ligation of the internal spermatic vein was adopted. This paper presents a critique of the varicocele syndrome and the results obtained in 25 cases.

PATHOLOGICAL PHYSIOLOGY

The venous drainage of the scrotal contents can be compared to that of the extremities. Both deep and superficial systems are present. This concept of dual drainage was first expounded by Ivanisevich⁵ in 1918, and is shown diagrammatically in Figure 1. His studies demonstrated a primary or deep system consisting of the internal spermatic vein, the ductus deferens vein, and the external spermatic vein. The latter two anastomose with the internal spermatic veins at the level of the external inguinal ring. The superficial or secondary drainage system was found to consist of the superficial and deep inferior epigastric veins, the superficial internal circumflex and the scrotal tributaries of the superficial and deep external and internal pudendal veins. These veins communicate freely with each other and with the primary system through the cremasteric branches of the external spermatic vein at the level of the external inguinal ring. The numerous convoluted veins of the pampiniform plexus coalesce as they course upward from the testicle until they become

one large vein in the upper portion of the inguinal canal. This, the internal spermatic vein, then traverses the retroperitoneal space to empty on the left side into the renal vein at a 90° angle and, on the right, to empty obliquely into the vena cava. Study of the lengthy internal spermatic veins⁶ has

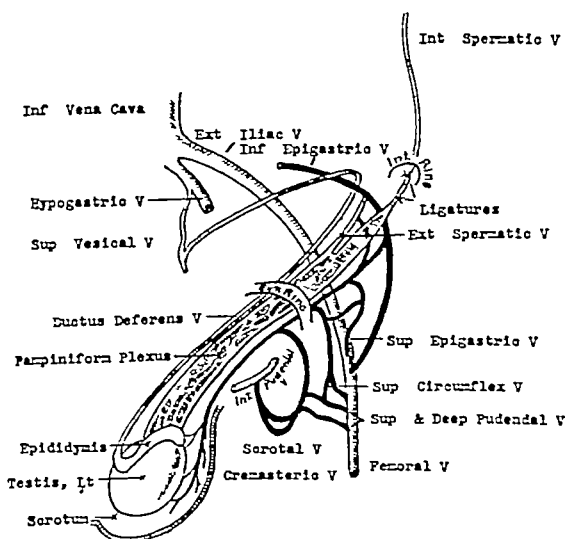


FIGURE 1. Diagram of the Venous Drainage of the Scrotal Contents (Adapted from Jarrett and Clark¹)

Primary system — internal spermatic, ductus deferens and external spermatic veins (in white). Secondary system — superficial epigastric, superficial internal circumflex and cremasteric veins, and through scrotal tributaries the superficial and deep pudendal and the internal pudendal veins (in black).

shown them to be devoid of valves except at their point of emptying. Congenital and degenerative changes lead to valvular deficiency. It is this combination of a long vein and valvular incompetence that constitutes the etiology of varicocele. This results in a retrograde flow down the internal spermatic vein, causing overdistention of the pampiniform plexus in the upright position. The reverse venous flow can readily be shown at operation. If a distal segment of the internal spermatic vein is occluded and the vein stripped proximally between the fingers, immediate refilling of the stripped portion is noted on release of the proximal finger occlusion. The marked preponderance of left-sided varicocele can readily be appreciated as being due

*From the Urology Section, Surgical Service, Cushing Veterans Administration Hospital.

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‡Formerly senior resident in urology, Cushing Veterans Administration Hospital.

Chief Urology Service, Cushing Veterans Administration Hospital.

to the mechanical disadvantage in preventing backflow offered by the right-angled junction of the spermatic and renal veins as contrasted to the oblique entrance of the right spermatic vein into the vena cava. Further study of the venous anatomy makes obvious the fact that the point of anastomosis of the superficial and deep systems, at the external ring, is of crucial importance. It was disregard of this anatomic feature that caused the failure of the low ligation procedure. Venous interruption at the external ring leads to disruption of both systems of drainage, with a poorly draining scrotum. Utilization of the more recent conception of venous drainage led to the ligation of the internal spermatic vein, which is physiologic and therefore successful.

CLINICAL PICTURE

It has been estimated that 10 per cent of males have varicoceles. Of this group 98 per cent are left-sided and approximately a third are actively symptomatic. The age group most frequently affected ranges from fifteen to thirty years. Consideration of the altered venous physiology involved allows one to predict the symptoms of varicocele. The patient notes gradually increasing scrotal enlargement and pendulousness during the course of a day of erect posture. This process is hastened by exertion. A sense of heaviness of the scrotum is followed by dull, dragging, aching, constant, pulling pain felt in both the scrotum and groin. The pain disappears slowly with rest in the supine position. In short, the pain is of the traction type caused by a heavy scrotum pulling on the spermatic cord. Other symptoms are to be viewed with the suspicion that they are due to other pathologic entities. Sharp or stabbing pain should cause one to suspect the concomitant presence of orchalgia, epididymitis or hernia. Occasionally, local venous thrombosis secondary to trauma may give sharp localized pain in the scrotum for a short time. Some explanation must be offered for small symptomatic varicoceles in view of many large ones that do not cause discomfort. It is our opinion that all patients with varicocele can be found to have symptoms, if closely questioned. The pain threshold is so variable that some patients are bothered more than others. Such variability of response is seen in many diseases. Although an overlay of psychiatric disturbance undoubtedly adds to the patient's degree of response to his disease, we do not believe that it is necessary to ascribe such an implication to every patient with varicocele.

Physical examination should do much to clarify the picture. The "bag of worms," scrotal pendulousness and asymmetry and enlarged, soft spermatic cord are familiar to all. Painful testis or epididymis does not belong in the varicocele syndrome, and should lead to suspicion of other etiologic factors. Javert and Clark¹ have shown the presence of co-

existent hernia in 25 per cent of their cases. The finding of hernia is much facilitated by examination in both the erect and the supine position. This allows more accurate evaluation of a possible hernial sac by fostering collapse of the distended vein while the patient is supine. In most cases, then, it should be possible to explain symptoms, whether severe or merely annoying, as due to varicocele, a coexistent varicocele and hernia or one of the ill defined syndromes of orchalgia or chronic epididymitis.

TREATMENT AND OPERATIVE TECHNIC

Although Ivanissevich⁵ recommended retroperitoneal ligation of the internal spermatic vein as early as 1918 this method was not appreciated in the United States until Bernardi, in 1942,⁴ reported his superior end-results from ligation at the internal inguinal ring. Present-day textbooks have as yet not assimilated the new literature and still offer a pessimistic outlook. Considerable emphasis is given to ascribing symptoms as due to overcongestion from unfulfilled sexual desires, scrotal fixation in psychoneurosis and other ill defined causative factors. Reassurance and the wearing of a suspensory are suggested as therapy. Surgery is considered unwise. The complications of the low ligation procedure—hemorrhage, painful thrombosis, testicular atrophy, epididymitis, hydrocele and recurrence—are admitted to be very frequent. The reason for this is now obvious. The procedure obstructs the venous drainage almost completely at the level where the anastomoses of the superficial and deep systems occur. It further fails to care for the gravity retrograde flow in the incompetent internal spermatic vein. The basic disorder is attacked at its source by the newer procedure, and the complications listed above are avoided. At the same time a concomitant hernia can be searched for. The region of anastomosis is spared. Adequate testicular suspension can be obtained.

The technic followed in this series varies only slightly from that described by Javert and Clark.¹ Through an oblique inguinal incision the external oblique fascia is split through the external ring to allow better exposure and a more effective herniorrhaphy. The spermatic cord is completely freed to the level of the internal ring. It is believed that this step allows for better eventual testicular suspension. The cremasteric fascia is opened longitudinally, and the internal spermatic vein isolated. Usually, one large vein, approximating a pencil in size, is found and is ligated at the internal ring, as is a secondary smaller vessel if present. In this series 15 patients had one vein, and 10 presented two veins, which in all cases were found to anastomose retroperitoneally. A 2-cm to 5-cm segment of the vein is excised, and the proximal end allowed to retract retroperitoneally. Careful search is then made for a hernial sac. If found, it is dissected free, and the sac ligated. It

is to be remembered that at this point forceful traction may pull down peritoneum and in so doing create a false sac that does not constitute a true hernia and does not need ligation.

Testicular suspension, which is next carried out, is considered very important for the final result. Three technics are followed: the distal vein stump is pulled proximally and sutured through the cremasteric fascia to the internal oblique muscle, the cremasteric fascia is closed transversely, and a further tightening of the lax spermatic cord is obtained by suture of the conjoint tendon under the cord to the shelving inguinal ligament. This lifts the cord by the mere presence of tissue beneath it. The external oblique is then resutured above the cord. Silk-suture material is used throughout the procedure. Postoperatively, the patient wears a suspensory for two weeks. He is allowed to be am-

On physical examination the varicocele was classified as large in 10 cases, moderate in 10, and small in 5. It was considered significant that 3 of 5 patients with small varicoceles had atypical symptoms. Only 1 patient was thought preoperatively to have a hernial sac. The incidence of hernia at operation was 12 per cent, with 3 small indirect sacs found. Moderately large lipomas of the spermatic cord were removed in 4 cases, and this proved to be the lesion present in the patient thought preoperatively to have a hernia.

The results have been grouped on a symptom basis to show the effect on prognosis of close evaluation of the symptom complex. A poor result was the case in which the patient continued to have scrotal pain even though it might vary in degree or type from the presenting complaint. In the typical symptom group of 21 cases, 20 were good re-

TABLE 1 *Results according to Type of Symptoms*

FOLLOW UP PERIOD	PATIENTS WITH TYPICAL SYMPTOM		PATIENTS WITH ATYPICAL SYMPTOMS		TOTALS	
	GOOD RESULT	POOR RESULT	GOOD RESULT	POOR RESULT	GOOD RESULT	POOR RESULT
MO						
3-6	6	0	—	—	6	0
6-12	2	0	—	—	2	0
12-18	9	0	—	—	9	0
18-24	3	1	1	3	4	4
Totals	20 (95%)	1 (5%)	1 (2%)	3 (7%)	21 (84%)	4 (16%)

bulatory on the first postoperative day and actually is eligible for discharge on or after the sixth postoperative day.

EVALUATION OF CASES

This series is small but does suggest certain trends in the varicocele syndrome. In 25 cases, the ages of the patients ranged from twenty to fifty-three years, and 20 were between twenty and thirty years old, which is in accord with the usually quoted figures of age frequency of symptoms. The duration of known scrotal enlargement showed a range of one to twenty years, with an average of four and two-fifths years. The duration of symptoms was much less, with a span of four months to five years and an average of two and a fifth years. Both enlargement and symptomatology showed a tendency to increase with time. Analysis of symptoms revealed that 21 of 25 patients had only the basic symptom complex of scrotal enlargement with dull, aching, dragging, scrotal and groin pain at the end of the day or after prolonged exertion. The pain was annoying as a rule, but in a few cases it was sufficiently distressing to require hours of bed rest for relief. The 4 atypical cases presented such variations as morning pain, sharp stabbing pain, localized scrotal pain, tender testes and intermittent attacks of pain. The effect of the type of symptoms on prognosis is discussed below.

Results over periods ranging from three to twenty-four months. In the case regarded as a failure, twenty months after operation the varicocele was gone, but scrotal and epididymal pain in intermittent attacks persisted. Study of the patients with atypical symptoms revealed 3 out of 4 to have poor results. All had small varicoceles. Over a twenty-month follow-up period, 2 were symptomatically unchanged, and the third had intermittent attacks of pain. The varicoceles were gone. All originally presented elements of sharp scrotal pain in addition to testicular or epididymal tenderness. Under our present criteria they would not be considered as candidates for this procedure. Table 1 shows the breakdown of cases in terms of follow-up period and type of symptom. It is to be noted that we learned early the futility of operation in the atypical cases. The large percentage of good results among the patients with typical symptoms further emphasizes the importance of early, careful evaluation. In view of the marked emphasis placed on psychogenic factors in the literature, it is interesting to note that a group of 4 patients were being or had been treated for psychoneurosis. All presented symptoms that were considered typical of varicocele. The surgical results were excellent in 4 gratified patients. We were encouraged by this experience to believe that, in spite of known psychoneurosis, typical varicocele

syndrome with a physiologic basis can occur and can be helped by appropriate surgical operation

The cosmetic results of high ligation have been completely satisfactory. All 25 cases showed a progressive shrinkage of the "bag of worms" from the day of operation to the completion of the process,

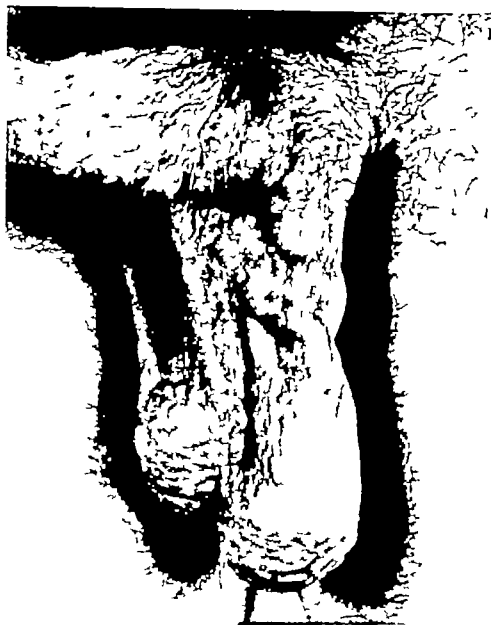


FIGURE 2 Preoperative Appearance, Showing the Engorged Pampiniform Plexus

usually within a month. Testicular suspension was very gratifying in that scrotal pendulousness was corrected as much as 4 or 5 cm. in some cases. All patients had scrotums that looked well within normal limits when the process of vein shrinkage, skin retraction and testicular suspension had reached its end point. Figure 2 and 3 show a typically good result.

This type of operative procedure was singularly free of complications. In 3 cases there were localized areas of slightly painful vein thrombosis, which disappeared within a month. No wound sepsis was present, and hematoma formation, testicular atrophy, hydrocele formation, epididymitis and scrotal induration were not noted.

SUMMARY AND CONCLUSIONS

The concept of dual drainage of the scrotal contents is reviewed.

A definite physiologic basis and type of symptom is postulated for the varicocele syndrome. It is stressed that symptoms not conforming to this pattern should suggest other disease as the source of the complaints.

The technic and rationale of operation are explained. A series of 25 cases showing 84 per cent good results is analyzed.

The opinion is stated and in part substantiated that the role of psychoneurosis in this condition has been overemphasized in the past.

The possible coexistence of hernia and varicocele is mentioned, and the facility with which both defects can be repaired in one operation explained.

The pessimistic attitude found in the literature regarding the results of surgery in the treatment of this condition does not seem warranted. On the basis of these results it appears fair to prognosticate that a patient with typical varicocele symptoms can be relieved of his scrotal distress and dis-



FIGURE 3 Postoperative Appearance
Note the lack of dilated veins

tortion by the high ligation technic with very little risk of operative complication. The operation seems contraindicated in atypical cases in which the varicocele is but an incidental part of another pathologic entity causing symptoms of its own.

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EOSINOPHILIA DURING INTENSIVE GOLD THERAPY*

EDWARD H. REISNER, JR., M.D.,† LYON LAPIN, M.D.,‡ AND OTTO STEINBROCKER, M.D.§

NEW YORK CITY

IN THE course of a study of intensive chryso-therapy with aurothioglycanilide (lauron) already reported,¹ serial hematologic observations revealed a constant and often striking increase in the eosinophil count, which is the subject of this report.

MATERIAL AND METHODS

Eighteen patients were treated with bi-weekly injections of gold. Sixteen received aurothioglycanilide (lauron), 1 received solganol-B oleosum, and 1 received myochrysine. The total dosage given ranged from 1 gm. to 10 gm. in a period of twenty-four to fifty-six days. Prior to every injection of gold, each patient received a complete

the amount of gold received or the duration of therapy (Table 1). The maximum eosinophil level occurred from ten days to fifty-six days after the start of therapy. In the patient who showed a count of 43 per cent during treatment an exfoliative dermatitis subsequently developed, but no other manifestations of toxicity occurred in the group. Although

TABLE 2 Eosinophil Responses and Toxicity in 33 Patients Treated with Gold on an Outpatient Basis

GOLD PREPARATION	NO. OF PATIENTS TREATED	PATIENTS WITH EOSINOPHIL COUNTS OF MORE THAN 5 PER CENT	NO. OF TOXIC REACTIONS
Aurothioglycanilide	15	9	4
Gold sodium thiosulfate	15	3	2
Other types	3	0	2
	33	12	8

TABLE 1 Range of Eosinophilia in Relation to the Dosage of Gold and Duration of Treatment in 18 Patients Undergoing Intensive Chrysotherapy

PATIENT	DRUG	AMOUNT gm.	EOSINOPHIL LEVEL		DURATION OF TREATMENT days	DAY OF MAXIMUM EOSINOPHILIA
			INITIAL %	MAXIMUM %		
A. L.	Lauron	10.0	2	9	49	22
R. A.	Lauron	10.0	5	6	56	26
L. D.	Lauron	10.0	0	17	49	45
A. W.	Lauron	10.0	2	17	50	13
C. S.	Lauron	10.0	1	5	49	15
G. K.	Lauron	10.0	1	43	49	31
M. A.	Lauron	10.0	2	22	49	31
J. S.	Lauron	10.0	0	15	45	39
A. C.	Lauron	3.0	2	5	56	24
H. B.	Lauron	3.0	2	10	26	16
B. H.	Lauron	3.0	4	9	24	19
R. C.	Lauron	3.0	1	6	37	27
A. T.	Lauron	1.1	2	9	45	19
E. F.	Lauron	1.2	1	11	38	10
H. K.	Lauron	1.1	2	12	38	29
V. H.	Lauron	0.9	4	8	35	21
A. M.	Solganol B	1.0	2	5	45	31
B. M.	Myochrysine	1.0	1	5	49	10

blood count, platelet count and prothrombin-time determination

RESULTS

No toxic reactions in the blood were observed with reference to any component. A constant increase in the eosinophil count was observed in every patient, and in all but 3 cases the maximum eosinophil count was in excess of 5 per cent of all white cells—a figure chosen as the upper limit of normal. The intensity of eosinophilia was not related to

there was no direct correlation between the amount of drug received and the degree or time of appearance of eosinophilia, the mean eosinophil increase for 8 patients receiving 10 gm. of gold salt was 14.9 per cent, compared with 6.2 per cent for 10 patients who received 3 gm. or less.

As a result of this experience the records of 33 consecutive patients treated with gold salts in the arthritis clinic as outpatients were reviewed, with reference to eosinophilia and toxic reactions. The results are shown in Table 2. Of 15 patients treated with aurothioglycanilide, 9 showed eosinophil counts in excess of 5 per cent, compared with 3 of 18 given other gold preparations. There was no significant difference in the frequency of toxic reactions in the two groups. The mean total dose of aurothioglycanilide employed was 1.99 gm., compared with 0.72 gm. of other forms of gold, chiefly gold sodium thiosulfate.

DISCUSSION

Eosinophilia as an accompaniment of chrysotherapy has long been recognized, and the subject is thoroughly reviewed by Sundelin.² Opinion is equally divided in the literature concerning whether or not eosinophilia is a contraindication to further gold therapy. Some observers regard it as a favorable prognostic sign.³ The most careful study is that of Sundelin, and his conclusions based on an analysis of 700 cases were that eosinophilia was no contraindication to further gold therapy, since it often subsided while therapy was continued. In

*From the Fourth Medical Division (New York University) Bellevue Hospital.
†Instructor in clinical medicine, New York University Postgraduate Medical School, assistant visiting physician, Bellevue Hospital.
‡Trubek Fellow in Rheumatic Diseases and assistant resident in medicine, Fourth Medical Division (New York University) Bellevue Hospital.
§Associate professor of clinical medicine, New York University Postgraduate Medical School, visiting physician, Bellevue Hospital.

patients with eosinophilia all kinds of complications of gold therapy were more prevalent, but in many cases the eosinophilia occurred after the complication and could not, therefore, be used as a warning of its imminence

Eosinophilia has been observed in the course of streptomycin therapy,⁴ liver therapy of pernicious anemia⁵ and the administration of many other therapeutic substances. It can be produced in animals by the injection of heavy metals.⁶ Some eosinophilia is a common occurrence in allergic and hyperergic states. It is generally accepted that the eosinophils play some role in the response to sensitization to foreign proteins. Recent reports suggest that this mechanism works through the endocrine system via the adrenal cortex.⁷ Steinberg⁸ has advocated serial bone-marrow studies during chrysotherapy as a guide to therapy. Since the significance of eosinophilia during gold therapy is still in question, we do not consider such a procedure warranted.

In our cases, although there was no direct relation in any case between the eosinophil level and the duration or intensity of treatment, the groups receiving larger amounts of gold showed a greater eosinophil increase. The frequency of eosinophilia was clearly higher in the patients receiving aurothioglycanilide, which again was probably due to the larger amounts of gold that were given with this preparation. In this short series of patients there was no greater frequency of toxicity in the aurothioglycanilide group despite the greater eosino-

philia. Our observations agree with the conclusions of Sundelin that although marked eosinophilia should excite caution it is not a contraindication to further treatment that is otherwise indicated.

SUMMARY

In 18 patients receiving intensive chrysotherapy, eosinophil counts from 5 to 45 per cent were observed in all cases.

This was not related to individual dosage or duration of treatment, but, as a general rule, the patients receiving more gold showed a higher mean eosinophil increase.

There was no direct relation between eosinophilia and toxic reactions, although the 1 case of exfoliative dermatitis encountered developed in the patient with the maximum increase of eosinophils.

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MEDICAL PROGRESS

NEUROPHYSIOLOGY, 1942 - 1948*

JOHN F. FULTON, M.D.

NEW HAVEN, CONNECTICUT

THE war years gave valuable impetus to studies on the nervous system, but few of the many important advances during these years stemmed from wartime research per se. The subject of neurophysiology has come to have such vast ramifications that it would be imprudent to attempt to cover the entire field in a brief review. I propose, therefore, to restrict this summary to the newer disclosures in the motor sphere. Developments in sensory physiology must be relegated to another occasion and a better informed reviewer, and likewise the many studies on the special senses, particularly the notable work on night vision carried out in Sweden, England and the United States. In planning the present summary I have followed in general the subject sequence of my monograph, *Physiology of the Nervous System*,¹ but I have included nothing described therein, except on occasion for historical setting.

MOTOR UNITS

In 1929 Denny-Brown² observed that when a single unit of a muscle, such as the cat's soleus, was activated, the muscle as a whole might develop as much as 10 gm of tension. In their classic paper on the motor unit published in 1930, Eccles and Sherrington³ obtained similar average values — that is, after maximal stimulation of the muscle and recording of the total tension developed, the motor fibers supplying the muscle were enumerated, by division of the number of fibers into the total tension, average figures were obtained of 5 to 10 gm for soleus, and as much as 30 gm for the medial head of the gastrocnemius. Clark⁴ counted the muscle fibers in the preparations that Eccles and Sherrington had used and found that each nerve fiber innervates from 100 to 150 muscle fibers, thus accounting for the relatively large tension capable of being developed by single ventral-horn cells. Eccles and Sherrington were aware of the fact that there were large differences in nerve-fiber diameters, and they assumed that the large fibers innervated large units and that the smaller ones probably innervated lesser units. They incidentally proved conclusively that the small fibers (some only 2 or 3 microns) come from the ventral horn and not from the sympathetic chain.

Recently, Kuffler and his associates,^{5, 6} working on frogs, have suggested that the small-nerve motor system of the skeletal musculature belongs to a special reflex group and that it can be activated independently of the large-fiber system. According to Kuffler et al., the large-fiber system produces the quick-twitch response with a single volley, whereas the small-fiber system causes appreciable muscle shortening only on repetitive excitation. The shortening is said to be "local" although considerable tension can be generated. The authors believe that a given muscle fiber may be innervated by both the small and the large fibers, but they add that this anatomic detail has not yet been conclusively demonstrated. They believe that, depending upon which fiber system stimulates the muscle, the muscle itself responds either with a local slow shortening or by a rapid shortening from a propagated disturbance. They draw the general conclusion that the large-fiber system is designed for rapid phasic movements, and the small-fiber for prolonged states of tension such as would be required for the maintenance of posture. Their hypothesis thus implies that a simple muscle fiber could be made to execute a sustained postural contraction at one time or a quick, all-or-none, twitch-like contraction at another.

Kuffler's observations as such are of considerable interest, particularly on account of his ingenuity in separating, both by reflex means and by compression of the nerve trunk, the large-fiber impulses from those of smaller diameter. The interpretations placed on the observations stand as a reversion to the long-abandoned dualistic theory of muscle function — that is, there are two sets of peripheral mechanisms, one for the execution of phasic movement and the other for postural tone, in the same muscle fiber. To be sure, many muscles have rapid white fibers admixed with slower-acting red fibers, and Denny-Brown⁷ clearly demonstrated that the slower red fibers are selectively employed for maintenance of postures, but they are activated in all-or-none fashion just as the white fibers.

An alternative explanation of Kuffler's findings suggests itself if the small-fiber system innervates fewer muscle fibers than the large-fiber system, one would anticipate that repetitive stimulation would be necessary to develop measurable tension at the tendon. This leaves unexplained Dr. Kuffler's claim

*From the Department of Physiology, Yale University School of Medicine.

†Visiting Professor of Physiology, Yale University School of Medicine.

that the action potentials developed at the end plates of the small-fiber system are not propagated. If this is borne out in future work, Kuffler and Gerard have presented the physiologic world with a conundrum that will occupy neurophysiologists for some years to come.

A more plausible explanation of the effects of small-fiber stimulation has been offered by Leksell,⁸ who has succeeded in selectively stimulating these small-fiber units (gamma fibers) in both cats and frogs. He was unable to detect any certain contractile effects that could not have been attributed to unblocked large fibers, but he found that with the muscle taut, stimulation of the gamma fibers had a definite effect on the afferent discharge from the muscle's proprioceptors.

Selective activation of the gamma fibers led to a considerable increase in afferent discharge provided the muscle was subjected to a certain amount of stretch. In slack muscles this effect did not appear. It is concluded that the gamma fibers serve as regulators of sensory activity originating in the muscle.

Sherrington, in 1894, had found that small fibers of the ventral roots innervated the muscle spindles. Until more forceful contrary evidence is presented than that offered by Kuffler et al. it seems reasonable to conclude either that the small motor fibers innervate the muscle spindles and thus regulate proprioceptive afferent discharge, as Leksell has suggested, or that they are all-or-none motor fibers innervating small skeletal-muscle units. The Kuffler-Gerard evidence that the small fibers are concerned with postural contraction except as they may influence the stretch receptors appears to me unconvincing.

Isolation of single units has also been achieved for human nerve and muscle by Kugelberg and Skoglund.⁹ Using two muscles, the first dorsal interosseus (stimulated through the ulnar nerve at the elbow) and the peroneus (stimulated through the peroneal nerve at knee level), they have been able to compare artificially evoked responses from nerve stimulation with the natural discharges of single motoneurons of the same muscle during voluntary contraction. They find, on nerve stimulation with slowly rising currents, that small spikes appear first, followed later by larger ones, which correspond to the units of higher threshold (and presumably of larger size).^{*} Precisely the same sequence was observed on volitional activation of these muscles—that is, small, low-threshold units discharged first, followed later by the larger, high-threshold units. The work of Kugelberg and Skoglund appears particularly significant since it indicates that some, at least, of the smaller units (which, one may assume, are innervated by nerve fibers of small diameter) give rise to all-or-none

contractions. This, however, does not preclude the possibility that others are concerned with proprioceptive regulation as Leksell⁸ has suggested.

THE SPINAL CORD

The human spinal cord was intensively studied during the war period owing to the large number of cases of spinal injury that came under observation in military establishments. During World War I a spinal transection was equivalent to a death sentence. A few patients survived for periods of a year or two as a result of fastidious nursing care, but the great majority succumbed to bedsores and ascending genitourinary infections within a few weeks of injury. Through the work of the late George Riddoch^{10, 11} in 1916–1917 the way was pointed for adequate care of such patients—how through the development of the bladder reflexes, the bladder itself could be kept free of infection and, through careful nursing, the skin could be kept clear and healthy. Now with the powerful adjunct of the sulfonamides, penicillin and streptomycin it has become possible to keep patients with spinal paraplegia healthy and free of infection for indefinite periods. With this therapeutic triumph has come increasing knowledge of the reflex status of spinal man.

Thanks to the work of Freeman,¹² Deaver,¹³ Munro¹⁴ and others who have studied more than a thousand cases of spinal injury during the war period, it is clearly established not only that flexor reflexes and mass withdrawal reactions return, but also that knee jerks and other strongly developed extensor reflexes may be regained and that they may be put to useful purpose in rehabilitating such patients and in making them ambulatory. During World War I it would not have been thought possible for a patient with complete spinal transection to become ambulatory and capable of attending to his own rectal and bladder functions. One of Freeman's patients, wounded in World War II, dresses himself in the morning, attends to his own toilet, swings himself on crutches into his own car and drives to work. Fiercely proud of his independence he declines assistance at any point of his daily routine. As a watchmaker he has an income of between three and four thousand dollars a year. In Dr. Freeman's series there are 30 other patients with spinal paraplegia that are similarly self-reliant and self-supporting. In the past there has been nothing more hopeless or pitiable than cases of spinal transection. Now, as the result of intelligent application of sound physiologic principles, such patients have reasonable hope for a useful life, and there are several authentic cases of women with complete spinal transection who have conceived and borne normal offspring.^{15, 16} Ambulation technics such as those described by Deaver, combined with diligent bladder care and other observances of detail in management, have enabled

^{*}Kugelberg and Skoglund⁹ are unwilling to commit themselves regarding whether there is a direct relation between spike size and unit size. Although such caution is commendable it would be contrary to all that is known of electrophysiology if there were not a direct relation.

more than half the patients with spinal injuries sustained in the war to find a place in society

Hope for promoting regeneration in the severed spinal cord still haunts the imagination of neurologists and neurosurgeons, and Freeman is of the belief that ways and means will be found to bring about voluntary control of musculature distal to a spinal transection. Sugar and Gerard¹⁷ report that they have obtained regeneration in the spinal cords of rats, but Davidoff and Ransohoff¹⁸ have been unable to confirm their results in cats. Brown and McCouch,¹⁹ similarly have failed to obtain evidence of cord regeneration in dogs and cats even when the cut ends of the cord were sealed together with prothrombin. The late Richard Meagher and Franc Ingraham, in unpublished studies, believed that they had bridged the gap in spinal pupes by planting an intercostal nerve rootlet from above the transection into the distal cut end of the spinal cord. Their histologic results were, however, unsatisfactory, and publication was on this account withheld. Freeman¹² describes a patient with transplanted spinal roots who has developed paresthesias and muscular twitchings in segments below the transection a year after operation.

THE THALAMUS

There have been few physiologic contributions to the knowledge of thalamic function since the publication of Earl Walker's²⁰ monograph, *The Primate Thalamus*, published in 1938. The projections to and from the dorsomedial nucleus of the thalamus and the rostral areas of the frontal lobes, and particularly from areas 9, 10, 11 and 12 of Brodmann and possibly from Walker's area 13 (Glees²¹), indicate that the dorsomedial nuclei are concerned with the effects induced by the operation of frontal lobotomy. Especially relevant in this connection is the fact that the operation has been used extensively for the relief of intractable pain, and it thus appears that the medial nuclei are in some way concerned with establishing the general character of pain reaction, but the precise nature of this relation remains to be worked out. After frontal lobotomy and the presumed degeneration of the dorsomedial nuclei that follows (Freeman and Watts²²), patients state that they still feel their pain but that it has ceased to bother them.²³

The large nucleus ventralis posterolateralis (VPL), which is the chief end station for the spinothalamic projections, has been studied in some detail by Chang and Ruch²⁴ in the spider monkey. Walker and others had previously shown a high degree of topographical lamination from the various spinal segments, the cervical being situated most medially and the sacral segment most laterally. The spider monkey, in addition to the usual lumbar segments, has three sacral roots and a caudal plexus usually made up of eight caudal roots that innervate the complex musculature of the prehensile tail. The

dendrites for the tail were carefully mapped by Sherrington's method of "remaining sensibility," and the degeneration resulting from dorsal root section and from section of caudal segments of the spinal cord were traced by Chang and Ruch²⁵ up the spinal cord into the dorsal column and into the thalamus. It was found that the large caudal projections to the thalamus were located in a sharply defined, comma-shaped area lying just lateral to the sacral projections (Fig. 1). Thus, in the spider monkey, one finds an even more precise topographi-

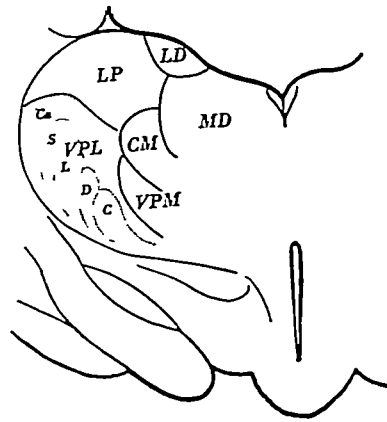


FIGURE 1 Diagram Showing the Topographic Arrangement in the Thalamus of the Spinothalamic Fibers from Different Levels of the Spinal Cord in the Spider Monkey

LP = nucleus lateralis posterior, LD = nucleus lateralis dorsalis, CM = centrum medianum, MD = nucleus medialis dorsalis, VPM = nucleus ventralis posteromedialis, VPL = nucleus ventralis posterolateralis, Ca = caudal projections, S = sacral, L = lumbar, D = dorsal (thoracic), C = cervical (Reproduced from Chang and Ruch,²⁴ with permission of the publishers)

cal representation in the thalamus than in forms that lack the extra prehensile appendage

THE HYPOTHALAMUS

There have been few notable advances in knowledge of hypothalamic function since the publication in 1940 of the hypothalamus volume of the Association for Research in Nervous and Mental Disease, except for the recent disclosures concerning sham rage and for certain developments in the sphere of heat regulation and metabolism

Sham Rage

Wheatley²⁶ has found that sham rage may be induced in enduring fashion in cats through placement of bilateral Horsley-Clarke lesions in the nucleus hypothalamicus ventromedialis — that is, in the infundibular or middle region of the hypothalamus. Lesions in this region also interrupt the large tract of pallidohypothalamic (Fig. 2) fibers, as well as part of the fornix column. Wheatley's animals behaved in closely similar fashion to those of Fulton and Ingraham²⁷ after bilateral prechiasmatic

lesions made by direct surgical interference. It was not clear from these studies, however, exactly what pathways or centers must be interfered with, but Wheatley's experiments have greatly reduced the possible alternatives. Kennard²⁸ has induced conspicuous sham rage in cats by radical removal of both frontal lobes, she also observed it in animals in which only the orbital surface was involved, but it is not clear from her protocols whether the rhinencephalon or its projections had been encroached upon.

Quite recently Bard and Mountcastle²⁹ have offered a highly significant body of data—if indeed they have not actually solved the major anatomic problem. They find it possible in cats to remove

expression are normally under the control of the olfactory center of the brain and that the hypothalamic centers normally governed by this region begin to discharge uncontrollably once connection is severed between them. It is not yet clear, however, how the autonomic centers in the neocortex correlate their activities with that of the rhinencephalon on the one hand, and with the hypothalamus on the other. As pointed out elsewhere in this review, there is evidence of close functional connection between the orbital surface—that is, area 13, which is a part of the neocortex—and the posterior hypothalamic nuclei, but there is still little evidence pointing to which nuclei in the hypothalamus receive projections from the rhinencephalon.

Kidney Function

Harris,³⁰ in a detailed study of the effects of stimulating the hypothalamus at the site of origin of the pituitary stalk (through the use of an implanted electrode activated by remote control), was able to induce in conscious rabbits sharp inhibition of a water diuresis, increase in urinary chloride and marked increase in estrus. These three effects could be duplicated by intravenous injection of posterior-lobe extracts. This is in keeping with the studies of Mary Pickford,³¹ who finds that application of small quantities of acetylcholine (for example, 8 microgm) to the supraoptic nucleus and to no other part of the hypothalamus causes prompt suppression of the diuresis through stimulation of the supra-opticohypophyseal system. The effect was augmented by eserine salicylate and removal of the pituitary body abolished it. These studies afford further evidence of the part that the nervous system plays in regulation of kidney functions.

Metabolic Functions

That other visceral and metabolic functions are regulated by the nervous system is also evident from the studies of Brobeck,³² who describes important neurogenic factors in the genesis of obesity. In his review he points out that Hetherington and Ranson, in 1939, succeeded in confirming beyond doubt the observations of Bailey and Bremer that lesions confined to the hypothalamus may produce obesity whether or not the pituitary body is damaged. Earlier studies had pointed toward the same conclusion, but of all those who investigated the problem, only Hetherington and Ranson were able to prepare animals with lesions that completely spared the hypophysis. Only their data, therefore, appeared unequivocal. After the appearance of Hetherington and Ranson's report, Brobeck³² began to study the nature of the deficit responsible for the obesity—that is, the source of the energy surplus that leads to the accumulation of the large quantity of fat. It now seems to be generally agreed that most of this extra energy is derived from ingestion of an excessive quantity of food, and that

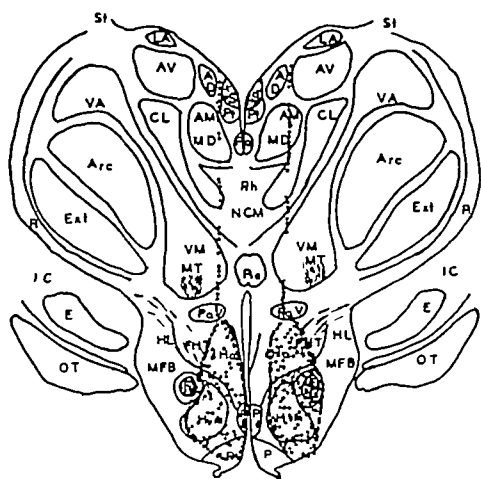


FIGURE 2 Diagram Showing Restricted Lesions in the Two Ventromedial Hypothalamic Nuclei (Hvm)

PHT=pallidohypothalamic tract, Ha=anterior hypothalamic area, MFB=median forebrain bundle, HL=nucleus hypothalamicus lateralis, PaV=nucleus hypothalamicus paraventricularis (Other abbreviations are explained by Wheatley²⁸ in his Figure 13)

the entire neocortex (both sides) and then observe that such a decorticate preparation shows no sign of anger or affect even when subjected to severe nociceptive stimulation such as pinching of the tail with heavy forceps. Unless the stimulation becomes exceedingly intense, the animal usually purrs, and its general behavior is that of an animal responding to pleasurable stimulation irrespective of whether the stimulus would normally be pleasurable or not.

If, however, the rhinencephalon is involved bilaterally, an animal that previously showed pleasurable reactions immediately shows the sham-rage pattern of behavior to any form of stimulation. These important findings, which were communicated in December, 1947, at the meeting of the Association for Research in Nervous and Mental Disease, indicate that the mechanisms of emotional

the most important deficit exhibited by the affected animals concerns their regulation of food intake. The degree of the obesity appears to be a measure of the severity of the overeating. This is true in all species thus far studied—in rats, cats, dogs and monkeys.^{23, 24}

There is, however, certain evidence that overeating, or hyperphagia, is not the only disturbance present, since certain animals with hypothalamic lesions tend to gain weight because of a depression of either basal heat production or energy output as locomotor activity. But Brobeck in 1946 found that neither of these changes contributes significantly to the development of obesity in animals fed ad libitum, inasmuch as both the basal heat production and total energy output tend progressively to rise above normal levels as animals become obese. Only when food intake is restricted do reduced activity and basal heat loss lead to an abnormal gain of weight.

Since lesions of the hypothalamus may interfere with regulation of each of the four factors involved in energy exchange—namely, food intake, activity, heat loss and body weight—it follows that the hypothalamus must be the level at which processes of energy metabolism are regulated and integrated by the central nervous system.

THE FRONTAL LOBES

No part of the brain has received a larger share of attention during the past five years than the frontal lobes. This has been due, in large measure, to the growing interest in the operation of frontal lobotomy, inaugurated in 1935–1936 by Egas Moniz, of Lisbon,²⁵ and introduced into the United States the following year by Freeman and Watts,²⁶ who in 1942 published their much discussed monograph.²⁷ The operation had its origin in a preliminary communication given in 1935 before the International Neurological Congress in London on the behavioral changes observed in 2 chimpanzees after bilateral removal of the forepart of the frontal lobes.²⁸ After the procedure the animals failed to exhibit frustrational behavior, temper tantrums and so forth, and Professor Moniz, on the basis of this admittedly imperfect evidence, concluded that interruption of the projection systems from the more forward of the frontal areas might relieve anxiety states in man. Removal of the forepart of the frontal lobes in the chimpanzees had been extensive, involving areas 9 and 10, and parts of 11 and 12 of Brodmann,²⁹ but it had not encroached upon the orbital surface, now designated areas 13 and 14 in Walker's³⁰ modification of the Brodmann scheme. From the experimental standpoint, therefore, there was no clear-cut indication of what part of the 9, 10, 11 and 12 complex need be removed to abolish frustrational behavior. It is also probable that areas 24 and 25 on the cingulate gyrus were involved,

the rhinencephalon thus being brought into the picture.

Despite absence of such basic experimental data, the lobotomists have gone ahead, and it is estimated that by January 1949 nearly 10,000 radical lobotomies had been performed in the United States and England and on the Continent. Penfield³¹ and his colleagues at Montreal,³² although recognizing the potential value of the operation, have been more conservative and have carried out a number of gyrectomies involving various parts of the frontal lobe in the hope of obtaining more precise evidence of the region concerned in the relief of anxiety states. His cases, as reported in December, 1947, are still too few to admit of precise evaluation, but it appears that areas 10 and 12 on the lateral surface have little influence, the more medial projections probably being the ones most intimately concerned.

Area 24

The anterior portion of the cingulate gyrus, known in the older literature as the anterior limbic area and in Brodmann's map as area 24 (Fig. 3), had

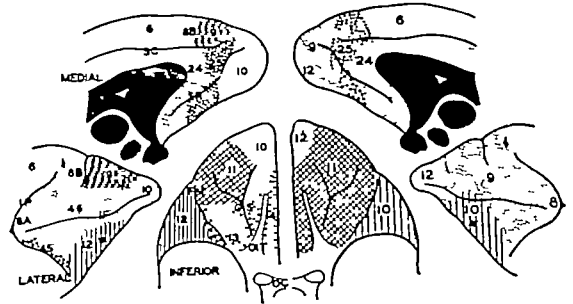


FIGURE 3 Walker's³⁰ Modification of Brodmann's²⁹ Map. Walker's cytoarchitectural map of the prefrontal lobe of *Macaca mulatta* (left) is compared with Brodmann's map of *Cercopithecus* (right). The numerical designations in Walker's map are derived from Brodmann's designations of comparable areas in the human cerebral cortex and hence do not necessarily have anything in common with Brodmann and Vogt's designations for the monkey.

been little studied until recently, but it was generally thought to be part of the rhinencephalon and therefore olfactory in function. Wilbur K. Smith³³ discovered that it had autonomic affinities, for on stimulation he obtained dilatation of the pupils, piloerection and cardiovascular changes that consisted of either an abrupt fall of pressure and slowing of the pulse or a slow rise with acceleration of the pulse, depending upon what part was stimulated. As with area 13, respiratory arrest generally occurred on excitation of area 24, with widespread relaxation of the skeletal musculature. McCulloch,³⁴ independently of Smith, had found that strychninization of area 24 led to relaxation of existing mus-

cular contraction, holding in abeyance of motor afterdischarge and suppression of motor response to stimulation of any motor focus in the cerebral cortex. Area 24 is thus to be classified with areas 4s, 8s and 2s as a powerful suppressor region. Smith also described vocalization as one of the effects of stimulating area 24, but this was not noted by McCulloch or by Ward⁴⁶ in his more recent study of the cingular gyrus. He has, however, confirmed Smith and McCulloch in all other details.

Ward⁴⁵ has also studied the effects of ablating area 24 in a group of monkeys. The behavioral changes were striking, and the animals after such a lesion, particularly if it were bilateral, appeared to lose "social conscience" thus

Immediately following either unilateral or bilateral subpial resection of the rostral cingular gyrus in the monkey there is an obvious change in personality. The monkey loses its preoperative shyness and is less fearful of man. It appears more inquisitive than the normal monkey of the same age. In a large cage with other monkeys of the same size, such an animal shows no grooming behavior or acts of affection toward its companions. In fact, it treats them as it treats inanimate objects and will walk on them, bump into them if they happen to be in the way and will even sit on them. It will openly eat food in the hand of a companion without being prepared to do battle and appears surprised when it is rebuffed. Such an animal never shows actual hostility to its fellows. It neither fights nor tries to escape when removed from a cage. It acts under all circumstances as though it had lost its "social conscience" [This is probably what Smith⁴⁶ saw and called "tameness"]. It is thus evident that following removal of the anterior limbic area, such monkeys lose some of the social fear and anxiety which normally governs their activity and thus lose the ability to accurately forecast the social repercussions of their own actions.

Ward has had the opportunity of making a similar lesion in a degenerated schizophrenic human being, and he believes that the procedure did as much for the patient as a more radical lobotomy would have done. Further studies on the effect of regional ablation of the cingulate are urgently needed both in animals and in man.

Area 13

More precise localizing data have been obtained for the posterior orbital gyrus (area 13) and for the medial orbital gyrus (area 14). In 1894 Spencer⁴⁷ had found that faradic stimulation of the orbital gyrus caused profound changes in respiratory movements and also in the level of the systolic blood pressure—this being true in dogs, cats, rabbits and monkeys. The studies of Spencer, however, were lost sight of until rediscovered by Bailey and Sweet⁴⁸ in 1940. Meanwhile, Bailey and Bremer⁴⁹ had shown that stimulation of the central cut end of the vagus nerve in the isolated head caused marked changes in the electroencephalogram of the posterior orbital gyrus and in no other part of the cerebral mantle. They concluded that this region of the orbital surface contained the chief central representation of the autonomic system. In 1943 Ruch and Shenkin⁵⁰ carried out bilateral ablations of area 13 and

found thereafter that the monkeys exhibited profound restlessness, pacing back and forth in their cages incessantly, when measured in activity cages, their motility was found to have increased 500 to 600 per cent.

More recently, Fulton, Livingston and Davis⁵¹ have confirmed Ruch and Shenkin's results on the effects of ablation, and Delgado,⁵² who studied their animals, has disclosed that skin temperature of the extremities and the ear lobes after bilateral removal of area 13 rises 8 to 10° and approaches the rectal temperature. In the light of this observation, Delgado suggests that the hypermotility that follows orbital gyrectomy may be a compensatory phenomena to assist in maintaining body temperature in the face of excessive heat loss. This release of vasoconstrictor tone must also cause a considerable decrease in peripheral resistance, which no doubt accounts for the rather striking falls in blood pressure that Freeman and Watts,³⁶ and others, have reported after their lobotomies—for in the Watts operation the line of incision passes down to the sphenoidal ridge and thus involves the posterior orbital gyrus. It has been suggested, indeed, that orbital gyrectomy may be the operation of choice for the relief of essential hypertension.

Equally significant have been the studies of Delgado and Livingston,⁵³ and of Livingston, Chapman and Livingston⁵⁴ on the effects of stimulation of area 13 in animals and man, particularly their disclosure of the importance of rate of stimulation. Wyss,⁵⁵ of Geneva, had found that the effects on respiration of stimulating the central end of the vagus nerve varied profoundly with the rate at which the nerve was stimulated, thus, at 70 per second, breathing movements could be arrested at expiration whereas at 20 per second inspiratory effects were obtained, at other rates respiratory movements could be made to increase in both depth and rate. Since there had been some discrepancies in the earlier reports on stimulation of the orbital surface, Delgado and Livingston,⁵² in the light of Wyss's observation, studied the effect of changing the frequency of the stimulus and obtained results corresponding closely with those reported by Wyss for the central end of the vagus. The responsiveness not only of area 13 but also of the cortex in the depths of the presylvian sulcus varies with frequency. Thus, the latter was entirely unresponsive at the higher rates (180 per second), but began to give responses at 60 per second (slowing), at 6 per second there was respiratory arrest in inspiration, and at 30 per second augmentation of inspiratory and expiratory amplitude.

It had been reported in man that the orbital surface was completely unresponsive to electrical stimulation (Penfield, Foerster and so forth). The importance of controlling frequency, however, had not been appreciated, and Livingston and his colleagues, after having negative results when they

stimulated the orbital surface with a 60-cycle stimulator, found striking respiratory effects, such as those seen in Figure 4, when they stimulated at 10 per second, the electrodes being of the needle concentric type, thrust down to the orbital ridge through a leukotomy burr hole (with the patient under pentothal anesthesia). Other details concerning the responses of the human orbital gyrus stimulation are found in the legend of Figure 4. It will be noted that respiratory effects can be separated from vasomotor effects, the latter being most conspicuously obtained from the more medial foci on the orbital surface.

The pathways from area 13 have still to be worked out, the main projection appears to pass through

are sometimes obtained on stimulation. Owing to its proximity to the olfactory nerve, it has been less carefully studied than the more lateral parts of the orbital surface. Fulton, Livingston and Davis⁵¹ noted that when the posterior part of area 14 was incised bilaterally, the animals (monkeys)

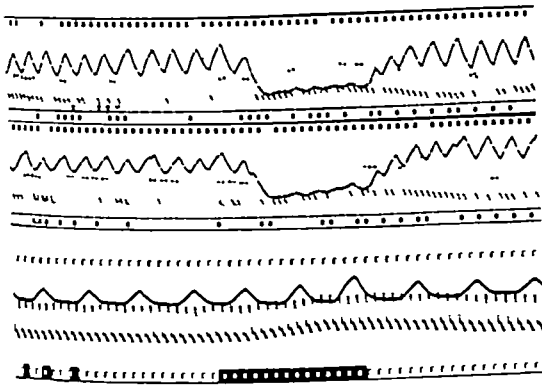


FIGURE 4 Photographic Record of the Respiratory and Blood-Pressure Response (Femoral Artery) to Stimulation of the Orbital Surface of Man under Light Pentothal Anesthesia

All stimulations are of ten seconds' duration and are at 10 cycles per second. The signal at the bottom of each strip identifies and defines onset and duration of stimuli. The first two strips show responses, from two different orbital loci, of prompt respiratory responses, from two different orbital loci, of prompt respiratory responses, from two different orbital loci, of prompt respiratory responses. The third strip shows the response in a region where no respiratory effect is obtained but where there is a moderate blood-pressure response. (Reproduced from Livingston, Chapman, Livingston and Kraitsir⁵⁴ with permission of the publishers.)

the anterior end of the internal capsule, and thence to the supraoptic nuclei of the hypothalamus. Glees⁵⁶ has made a preliminary study of the anatomic degenerations following lesions in this region, and a large proportion of the fibers appear to be unmyelinated. Ward and McCulloch⁵⁷ find that when strychnine is injected into the orbital surface, the supraoptic nuclei, as well as some of the posterior hypothalamic ones, become specifically activated (Fig 5). It thus seems probable that area 13 has primary subcortical connections with the hypothalamus.

Area 14

Less is known about functional localization in area 14 (medial orbital gyrus). Vasomotor responses

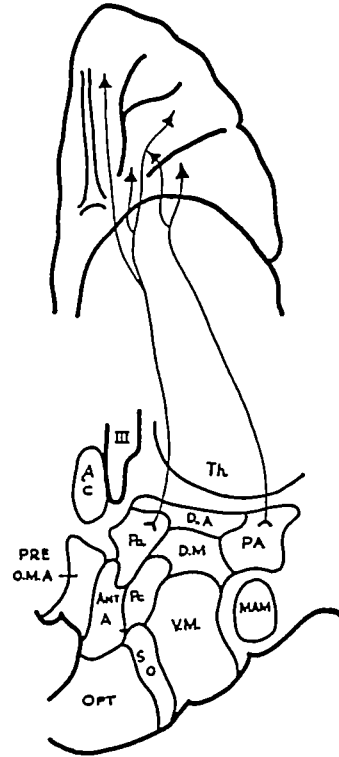


FIGURE 5 Diagrammatic Representation of Homolateral Projections from Areas 13 and 14 (Orbital Gyrus) of the Monkey to the Hypothalamus

Pa = paraventricular nucleus, PA = posterior hypothalamic area (Other abbreviations are explained by Ward and McCulloch⁵⁷)

develop conspicuous sham rage similar to that described after corresponding lesions in cats by Fulton and Ingraham²⁷. In their recent analysis of sham rage, Bard and Mountcastle²⁹ observed that the entire neopallium can be removed without the appearance of sham rage so long as the rhinencephalon remains intact. If, however, the rhinencephalon is encroached upon bilaterally, even though the neocortex remains intact, sham rage invariably occurs. It therefore appears that lesions of the posterior part of area 14 must interrupt projections to and from the rhinencephalon. Sham rage has not been encountered after bilateral lesions of area 13.

The fact that the orbital surface was spared in the 2 chimpanzees on which the operation of frontal lobotomy was based and the fact that profound autonomic changes develop when area 13 is involved and further that sham rage may follow posterior

lesions of 14, suggest that in the operation of frontal lobotomy, the orbital surface should be spared. The work of Ward indicates that more attention should be given to the specific function of the cingulate gyrus, which is known to be intimately associated with the olfactory center of the brain and hence with the emotional life of man.

Renal Circulation

It was pointed out above that the supraoptic nuclei in the hypothalamus regulate tubular reabsorption of the kidney through controlling the secretion of the posterior pituitary body, and it has recently been shown that the nervous system also regulates the renal circulation. Trueta and his colleagues^{58, 59} have discovered that the glomerular circulation can be shunted reflexly into the medullary vessels of the kidney and so completely abolish urine formation. Cort⁶⁰ has proved that this renal shunt can be activated in the spinal animal through stimulation of any large sensory nerve, the reflex being abolished by section of the lesser splanchnic nerve. He finds, moreover, in cats that the shunt can be activated by stimulation of the vasomotor center in the medulla, the posterior hypothalamic nuclei and also areas 13 and 6 of the cerebral cortex. This clearly provides a physiologic explanation of emotional anuria.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 35221

PRESENTATION OF CASE

A thirty-nine-year-old woman was admitted to the hospital complaining of grossly bloody urine accompanied by small clots for one week.

During the same interval urinary frequency, dysuria and nocturia were present. In the week before admission she also had severe right-costovertebral-angle pain on motion of the right leg. There had been no leg edema, and no weight loss.

Her general health had always been good except for one episode of slight hematuria four years before admission.

Her menses were regular, with twenty-eight-day intervals. There had been no bleeding between periods, except for a two-week period two months before admission, when she bled "off and on."

Physical examination showed a nontender right-upper-quadrant mass. On pelvic examination a small mass was palpable on the posterior aspect of the uterus near the top.

The blood pressure was 120 systolic, 70 diastolic. The temperature was 98.8°F, the pulse 112, and the respirations 24.

The white-cell count was 6900, with 79 per cent neutrophils, 15 per cent lymphocytes, 3 per cent monocytes and 3 per cent eosinophils. The hemoglobin was 7.5 gm.

The specific gravity of the urine was 1.015, with a $++$ test for albumin. The sediment contained 50 red cells and 25 white cells per high-power field. The urine culture was negative. The nonprotein nitrogen was 17 mg per 100 cc.

On intravenous pyelography the kidneys were within normal limits as to size, shape and position. There was a soft-tissue swelling at the hilus of the

right kidney, which appeared to be due to dilatation of the pelvis. After intravenous administration of dye it was excreted promptly, outlining nonobstructed urinary passages on the left. Excretion on the right was slower, and there was dilatation of the calyces on the right. The large, dilated pelvis showed only a small amount of dye in its margins, which suggested that the pelvis and the bases of the calyces were filled by nonopaque material. The right ureter was not visualized. The bones of the lumbar spine and pelvis were not remarkable.

On the third hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. SAMUEL VOSE: The picture of this case as presented in the abstract is that of a woman very seriously ill who had a mass in the region of the right kidney, gross hematuria and what was presumably an acute anemia (hemoglobin of 7.5 gm), with a negative past history referable to the urinary tract except for one episode of slight bleeding four years previously and a small amount of vaginal bleeding two months prior to entry into the hospital. The bleeding must have been very severe to reduce the hemoglobin to this point. The laboratory findings are not particularly helpful except to demonstrate that she had anemia, and the intravenous pyelogram showed a filling defect in a hydronephrotic kidney.

Gross hematuria is one of the most important and interesting conditions that occur in disease of the urinary tract. Since there are some forty-odd causes for it, it is sometimes difficult and always interesting to try to figure out. One of the three factors involved in a situation such as this regards the source of bleeding. In this case there is no definite evidence of the source. Dr. Colby told me that cystoscopy showed clear urine from both ureters. We assume that the bleeding was coming from the right kidney, but actually that is an assumption rather than a fact. Recently we had a patient with bright-red blood spurting from the right ureter. An intravenous pyelogram showed a left ureteral calculus. If the bleeding had not been seen we would have assumed that it was coming from the left kidney. The only reasonable assumption here is that it was coming from the right kidney, which presumably was the mass in the right side.

As to the cause of the blood, assuming its source to be in the kidney, this was in all probability acute

surgical bleeding. There is no evidence of nephritis—no casts in the urine and nothing in the history to indicate blood dyscrasia. Of this surgical group there are three main causes, traumatic, inflammatory and neoplastic. There is no history of trauma and no evidence on the x-ray film of stone, and a traumatic origin is not likely. Many of the acute inflammatory bleedings are from a hemorrhagic type of cystitis. Dr. Colby tells me that the bladder was normal. Pyelonephritis of some type must be considered. Inflammatory bleeding usually is not of the profuse type that we see here. The bladder is ruled out, but certainly a tumor of the kidney, either cortical or pelvic, must be seriously considered.

In analyzing a few of the symptoms, we see that she did have an attack of acute pain in the costo-vertebral angle, which always brings up the probability of an obstructive lesion of some sort, which might be blood clot or primary hydronephrosis. Certainly, there was some obstruction. She had no evidence of fever or chills, to indicate an acute inflammatory condition as a probable cause of pain. The previous bleeding, of course, is somewhat in favor of neoplastic disease. It does not seem possible, however, that blood would occur from a neoplasm and not recur some time during the four-year period since she had had trouble. The bleeding from the vagina reported two weeks prior to entry is difficult to explain except on the basis of the vaginal examination, which showed a small mass in the posterior surface of the uterus, probably a small fibroid. There may have been others that caused bleeding. That is purely speculative. It does bring up the remote possibility of endometriosis. That is unusual in the kidney—probably it is more common in the bladder. Perhaps we cannot rule it out completely. On physical examination the mass in the right upper quadrant was not tender at the time of examination. Evidently, the acute obstruction that caused the pain had been to some extent relieved.

The laboratory work shows one interesting finding, a negative culture on the urine, with a few white cells and red cells. A negative culture in the presence of white cells or other evidence of infection always raises the question of tuberculosis. We have to have more evidence one way or the other to know whether this was present. That is not too important to answer so far as the acute difficulty is concerned, and apparently it was not something that entered the minds of the men in charge as a likely probability.

Will Dr. Wyman show us the x-ray films?

DR. STANLEY M. WYMAN: The right kidney is fairly well outlined on the plain film. There is no evidence of stones. Intravenous dye appears promptly on both sides. Dilated calyces are seen, and there seems to be definite thinning of the cortex of the kidney lateral to the dilated calyces. What

appears to be a large pelvis is also imperfectly outlined. Within the pelvis and all the calyces there are multiple, round, rather smooth, lobulated, filling defects. The left kidney appears perfectly normal as far as can be seen.

DR. VOSE: In the standing position the right kidney drops well down below the iliac crest. Here is a kidney that was definitely hydronephrotic and undoubtedly had been for a good many months, probably years. The cortex is very thin. One can hardly see it, and this is something that does not take place in a short time as in an acute hydronephrosis. The filling defect may be a part of the cause of hydronephrosis, or it may be secondary to the hydronephrosis. My opinion is that it is secondary, that the hydronephrosis has been there for many years, and that the condition that caused the bleeding is of apparently recent origin.

This comes down to two or three conditions: tumor in the pelvis, nonopaque stone or hydronephrosis with secondary inflammation and bleeding with collection of blood clots in the kidney pelvis. There is also the outside possibility of tuberculosis. There is a little bit about the pyelogram that suggests a necrotizing papillitis, but she does not appear to have been ill enough to have that. There is no history of diabetes and not enough cortical necrosis to be consistent with that diagnosis. There is a possibility of some rare type of cyst in the kidney pelvis, but I think that tumor, nonopaque stone and a blood clot are the most likely causes of the filling defects. It is almost a toss of the coin to determine which one. I would bet on primary hydronephrosis due either to intrinsic disease in the upper ureter or at the ureteropelvic junction or to a very low kidney with an abnormal implantation of the ureter with secondary infection and hematuria as my first guess, papillary tumor of the renal pelvis as my second, and nonopaque stone as the third.

DR. FLETCHER H. COLBY: I think that Dr. Vose came as close as he could in this bizarre picture. Our preoperative diagnosis was papillary tumor of the renal pelvis. We decided that that was the most likely diagnosis in view of the fact that while this kidney had numerous rather large filling defects present in the upper portion, renal function was sufficiently well preserved so that the kidney excreted the dye in reasonably good concentration. Therefore, neoplasm involving the pelvis and not the parenchyma was more likely. The kidney was approached through a thoracoabdominal incision, and with that exposure the entire kidney and the renal blood supply were readily accessible. The kidney was enlarged, and the pelvis dilated, and through the pelvis one could feel round, rather soft masses. One of these masses was felt a little bit below the ureteropelvic junction. Believing that we were dealing probably with a primary tumor of the renal pelvis, probably papillary carcinoma,

we enlarged the incision and removed the entire kidney and ureter intact with a portion of the bladder wall

CLINICAL DIAGNOSIS

Papillary tumor of renal pelvis

DR VOSE'S DIAGNOSIS

Primary hydronephrosis, with secondary infection and hematuria?

Papillary tumor of renal pelvis?

ANATOMICAL DIAGNOSIS

Hamartoma of cloacal tissue in renal pelvis

PATHOLOGICAL DISCUSSION

DR TRACY B. MALLORY The specimen brought to the laboratory was entirely unlike anything that I had ever seen. The entire pelvis was filled with these polypoid masses, which had a myxomatous, almost gelatinous character. My thought was that

clearly characteristic of Brunner's glands, others looked like small-bowel epithelium, with numerous Paneth cells present, and some looked like large bowel. None of the ordinary textbooks of pathology contain descriptions of such a tumor and in a long review of renal tumors by Melicow,¹ based on 199



FIGURE 1

they must consist of myxomatous tissue. The large tumor appeared to be attached to the renal pelvis in two spots, and there was an entirely separate tumor a short way down the ureter, which can be seen at the extreme left of the picture. When the microscopical sections came through they were most surprising and confusing. The tumor consisted of multiple acini of varying size embedded in an abundant fibrous myxomatous stroma. The acini were quite variable in character, some of them were lined with transitional epithelium of the usual type seen in the urinary passages, and others with obviously intestinal types of epithelium, some were



FIGURE 2

cases, nothing similar was reported. However, in the collection of material in the registry in the Army Medical Museum² they do have such tumors both in the bladder and in the renal pelvis. The explanation that has been offered and seems reasonable is that they arise from fetal nests of cloacal tissue. The cloaca of fetal life eventually separates and differentiates into the urinary passages anteriorly and the bowel posteriorly two ways, into intestinal epithelium or into transitional epithelium. That is I believe the most reasonable explanation of the tumor. I think it is entirely benign as far as one can judge from our usual microscopical criteria, and I believe that this other tumor part way down the ureter represents a second lesion of the same type rather than extension or metastasis from the renal tumor. It is difficult to know what exact name to attach to it. I would call it a hamartoma of cloacal tissue.

DR COLBY Quite a number of years ago we had a tumor in the bladder that histologically, as

far as I remember, was identical, or very nearly so, to this. It consisted of myxomatous tissue in which there were mucous secreting glands with no evidence of cancer. We classified it as an embryonic rest in a urinary bladder.

DR MALLORY: Tumors similar to this can occur throughout the length of the urinary tract, in the bladder, ureters and pelvis of the kidney, and also can be found extending up the urachus even to the umbilicus.

DR LAMAR SOUTTER: Will the tumor metastasize?

DR MALLORY: I would not expect it to. It is such an unusual tumor that I am rather hesitant about being dogmatic about its degree of malignancy, but from the usual microscopical criteria I would not think it was malignant.

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CASE 35222

PRESENTATION OF CASE

A forty-nine-year-old Italian housewife was admitted to the hospital because of an epigastric mass.

The patient's first admission to the hospital occurred twenty-three years before, when she gave a story of diarrhea and bloody stools of eighteen months' duration. Physical examination was not remarkable, but proctoscopy showed diffuse redness and ulceration of the mucous membranes as far as could be seen. A diagnosis of ulcerative colitis was made, and a double-barreled ileostomy was done, with considerable improvement. She continued to have occasional abdominal cramps and discharged bloody mucus by rectum for five or six years, but this gradually subsided until she was passing only a small amount of mucus by rectum every few weeks. The mucous discharge usually occurred during a cold. Eight years before the present admission she developed an empyema of the right chest following an unresolved pneumonia caused by Type III pneumococcus. Rib resection and drainage were required. Approximately two years prior to the present admission she noted a tight feeling and felt a lump just below the umbilicus. The mass did not increase in size during this period and produced no symptoms.

Physical examination revealed a well developed and well nourished, co-operative woman. The scar of the rib resection was well healed. There was a Grade II basal systolic murmur. The ileostomy in the right lower quadrant was in good condition. In the region of the umbilicus and extending to the left was a nontender, 5-cm. mass, which although slightly attached to the anterior abdominal wall

seemed freely movable. The ileostomy located to the right and below the umbilicus functioned well. Pelvic examination was negative.

The temperature, pulse and respirations were normal. The blood pressure was 130 systolic, 85 diastolic.

The urine showed a specific gravity of 1.014 and was entirely normal. The hemoglobin was 10 gm., and the white-cell count 10,000. A barium enema could not be done because of the severe pain that it caused. Films of the abdomen and intravenous pyelograms showed a peculiar layer of calcification that was seen in a semilunar fashion to extend to the left of the upper lumbar spine and suggested the margin of the calcified tumor. The left kidney was normal in size and excreted the dye in good concentration. The right kidney was rather small and hypoplastic and showed delayed excretion with rather wide calyces and pelvis filling one or two hours after the injection of dye. The right ureter was not well visualized. There was a suggestion of a mass in the right side of the pelvis and right side of the abdomen. A chest film showed some elevation of the right leaf of the diaphragm, with pleural adhesions that caused slight limitation of motion. There were old partial resections of several right ribs. There was some fibrosis, and increased markings in both lungs, mostly on the right. There was some thickened pleura over the right chest laterally. The heart shadow was not enlarged, but there was rather marked tortuosity of the aorta.

After preparatory transfusions an operation was performed on the sixth hospital day.

DIFFERENTIAL DIAGNOSIS

DR CHARLES G. MIXTER: This type of exercise is interesting and sometimes amusing to the audience but puts the discussor on the hot seat because there is a cat in the meal somewhere. I am sure that there is a festive feline lurking around here that is going to get me into trouble. "Films of the abdomen and intravenous pyelograms showed a peculiar layer of calcification." I suspect that that may be the cat in the meal.

We might make a brief review of the past history to see if we can find anything that might have a bearing on this patient's mass. In the first place she was an Italian, of about fifty years, and she had a history of ulcerative colitis that ran a more or less characteristic course requiring operation, and then presumably the large bowel quieted down and had remained more or less quiescent. That I think we should put aside for future discussion because it might have some bearing on the differential diagnosis. I believe we can forget about empyema following an unresolved pneumonia as far as the differential diagnosis is concerned, because I do not see how this would have any bearing on the mass at the umbilicus. It is true occasionally, and I have seen it in children, that a chronic empyema may

descend through the diaphragm and find a point at the umbilicus, but this case certainly would not fall in that category

The next thing to discuss is the abnormality of the kidney. The mass was on the left. The right kidney was a hypoplastic type of kidney with delayed excretion, and yet the urine was normal without anything of consequence in the sediment. That to my mind perhaps suggests a hypoplastic kidney, possibly of congenital origin, and I do not believe has anything to do with this picture. We might consider some retroperitoneal mass from the wolffian ridge, but this being on the right side and the tumor on the left makes it unlikely. Furthermore it presumably was attached to the anterior abdominal wall.

Perhaps it is all right to ask if a blood Wassermann or Kahn test was negative. Also, I should like to know about the gastrointestinal series, the gall-bladder studies or lateral films and whether the patient had a peritoneoscopy.

DR TRACY B. MALLORY: At the first entry, twenty-two years previously, the blood Wassermann test was negative. Dr. Wyman can show the x-ray films at any time.

DR MIXTER: I would like to see them. The patient had tortuosity of the great vessels, and, of course, we have to consider in the differential diagnosis an aneurysm but it is hard to link that up with slight fixation of the anterior abdominal wall. Certainly, no mention is made of pulsation.

DR STANLEY M. WYMAN: The chest films show the old defects in the right ribs, old pleuritis and a somewhat tortuous thoracic aorta. I can see no evidence of active disease in the chest. There are a few scars in the right-upper-lung field, which are possibly due to old tuberculosis. The calcification described lies in linear fashion, is somewhat lobulated, is situated just to the left of the third lumbar vertebra and extends over a distance of perhaps 5 or 6 cm. The right kidney shadow can be seen; it is very small. The left kidney is long and rather slender.

DR MIXTER: I believe that the calcification has considerable bearing on the differential diagnosis.

DR WYMAN: The later films from the pyelogram show the very small right kidney to have excreted a small amount of dye of poor concentration at the end of two hours and the calyceal system is greatly dilated, suggesting possibly an old infectious process. There is some soft-tissue density in the right pelvis, which is hard to define accurately but is present on all films. I am unable to say what it is. I cannot define it very well, but it may be linked up with this trouble in the right kidney.

DR MIXTER: What is this shadow?

DR WYMAN: The lower margin of the liver.

DR MIXTER: Is there any gross deformity of the bladder?

DR WYMAN: The bladder seems to have a fairly normal contour. How much of the shadow in the right abdomen is due to the ileostomy, I do not know.

DR MIXTER: The pelvic examination was reported negative. That, however, does not necessarily rule out a pedunculated mass.

Let us take a brief survey of the possibilities. In the first place I think that we can rule out any acute infection. The temperature, the patient's general condition and the duration of the illness over a period of two years are against anything of that nature. Furthermore, I think we can rule out cancer in all probability because the condition was stationary over two years. The patient did not show the inroads of a malignant process, although we have to bear in mind that carcinoma is a fairly frequent complication of ulcerative colitis — much more so than in the normal bowel. I believe we can rule that out also.

That boils it down pretty much to consideration of possible masses in the umbilical region. Let us first consider the masses that do not necessarily or frequently show calcification, because although that is suggestive it may lead us astray. The first one that comes to mind is the leiomyofibromatous type of tumor of the gastrointestinal tract, even a gastric tumor that has grown outward from the serosal surface might be located in this position, and sometimes remains very quiescent. But I still believe that this calcification is of sufficient importance so that I would not consider that diagnosis.

Fecal masses should be considered in all differential diagnoses, but here is a woman who had an ileostomy. Fecal masses almost invariably occur in the large bowel. Continuous pressure over a fecal mass will cause indentation almost invariably. We have none of the obstructive signs that would be present with a fecal mass, and it certainly would not persist over a period of two years. There are rare tumors, especially urachal cysts that occur below the umbilicus and are attached to the abdominal wall, it is true, but they are not freely movable. I think from the mobility of this tumor we can rule out any lesion within the anterior abdominal wall or anything too intimately in contact with it. There are omental and mesenteric cysts. It is true that all cysts may deposit a certain amount of calcium, and that may be true of omental and mesenteric cysts, but in my personal experience I have never encountered it and I believe it must be rare to find calcium deposits in such cysts. It is true that my experience was almost exclusively in children, in whom one would not expect to find calcareous deposits perhaps. They are silently growing and are generally brought to one's attention simply as an abdominal mass. They are freely movable, except when they reach enormous size, as particularly the mesenteric cysts. They usually occur in the upper small bowel, and often are dumb-

bell in shape Pancreatic cysts and liver cysts, particularly pancreatic cysts, may form calcareous deposits, but one would expect fullness in the epigastrium, certainly that is true of simple cysts of the liver I have seen one simple cyst of the liver that presented as a definite epigastric mass, which descended on respiration, and it would not fit into this category It is true that Meckel's diverticulum can attain enormous size, but it is not palpable except when it is accompanied by acute inflammatory reaction or perforates and forms an abscess So there again I think we can rule that out Let us now consider tumors that may be associated more commonly with calcification First let us consider calcified mesenteric glands Here we have, however, central foci that do not show a crescentic linear type of calcification that we see here Furthermore, a gland of this size would certainly be unusual Perhaps we should mention lithopedium, although the x-ray appearance would be different, and I think that is a far-fetched possibility We have to consider echinococcal cyst, a wandering cyst might be located in this region It is not uncommon to get a linear calcification, and this woman was an Italian There is no record of a complement-fixation test available

Hematomas may show calcification — although the calcification is usually more or less fuzzy and diffuse rather than linear

A gallstone may be palpable, and I have here one that I removed some years ago It is an interesting specimen and was readily palpable I could move it about the abdomen It made a perfect cast of the gall bladder In the case under discussion one would have to suppose that it had ulcerated through the gall bladder, wrapped itself in the omentum and worked its way down to the umbilicus The calcium deposit on the surface could well follow this type of shadow I think that is far fetched Calcification is frequently associated with any form of chronic abscess or infection

One thing we must consider is a pocket in the old ulcerative colitis that she had years previously, with a chronic abscess as well as calcification We cannot rule it out We have to consider other likely diagnoses

I do not believe this was a foreign body lying within the intestinal lumen It is true the human being is capable of all sorts of aberrations, and any cavity within the body may be a suitable receptacle for a foreign body Some of us have seen hairpins

introduced into the female bladder, and I have taken a rivet out of the male bladder But a foreign body introduced through an ileostomy would probably not stay in the intestine for nearly two years without either being extruded or causing difficulty On the other hand this patient was operated on twenty-three years before this admission I do not know what the sponge-count report was, but one of the things I have strongly in mind is that she had a sponge wrapped up in the omentum that caused this linear calcification such as we see in this film Sponges can lie quiescent for years I have removed one that was a movable mass in the abdomen, in a woman who had had an ovarian cyst removed some three or four years before The sponge had rolled itself up in the omentum and lay dormant over that period A sponge can show calcification of this type

Another calcified tumor that we must consider is uterine fibroid, pedunculated, or one that from torsion had separated by necrosis and then become engrafted at some other site, perhaps near the umbilicus Such tumors may show calcification of this type Another definite possibility is a pedunculated ovarian cyst, because ovarian cysts are prone to show a fine linear calcification I think I am right on that from the x-ray standpoint.

DR WYMAN Sometimes

DR MIXTER Particularly the dermoids have calcification that might follow this pattern

Time is drawing to a close and I must end my discussion, but I would say that there are three diagnoses I would particularly like to consider as possibilities I do not believe I would want to commit myself any further than that On the law of chances I would say first that this might be a foreign-body cyst, second, a dermoid, and third, a fibroid I believe the time is up, and as the old saying goes you never can tell what is in the box before you take the cover off I would like to know what operation showed

DR MALLORY Dr Warren, will you tell us your opinion and operative findings

DR RICHARD WARREN Our reasoning was not so astute as Dr Mixer's We had however more information that I am afraid did not get into the record There were two or three points that swayed us The first was that the patient had not had any passage of material by rectum for several years The record states that there was mucus passed every few months but that was inaccurate The

second point was that rectal examination was impossible because there was a complete block at the internal sphincter. Tying these facts together with the mass that was palpable in the region of the umbilicus we began to think this was inspissated material—accumulated colonic secretions. We could not explain the calcification. That bothered us a great deal.

CLINICAL DIAGNOSIS

Inspissated material in colon

DR MIXTER'S DIAGNOSIS

Cyst, due to foreign body

ANATOMICAL DIAGNOSIS

Mucocele of large bowel due to strictures in ulcerative colitis of defunctioned bowel

PATHOLOGICAL DISCUSSION

DR WARREN: We operated on the patient and found that she did have a greatly distended right colon—greatly distended with a mucoid type of material. The defunctioned terminal ileum was also distended to the same diameter as the colon. The material was under such tension that it was coming out through the interstitial spaces. Most of it was in the right colon, although there were patches on the left side as far down as the lower segment. This material was incarcerated in several

compartments. The lumen of the colon at the rectal end was closed off as it was at the defunctioned end of the double-barreled ileostomy. It was interesting also that the patient had had acriflavine colonic irrigation for a year or so following ileostomy.

DR MIXTER: I am surprised there was not a palpable, putty-like mass in the right side of the abdomen.

DR MALLORY: This picture shows the entire colon here and the terminal portion of the ileum, which, as one can see, is dilated almost to the size of the colon. The next picture shows the bowel after it was opened and here is one of these huge masses of inspissated secretion. As one passes along to the sigmoid there is another mass of mucus, not quite so large. The mucus, as Dr Warren said, had partially split the wall of the bowel so that we found mucus all through the layers of intestinal wall. This caused us considerable worry at first for fear we were dealing with colloid carcinoma, in which tumor cells may be very infrequent and one finds only great masses of mucus. Here and there, however, we could find remnants of intestinal epithelium, which were quite normal—not neoplastic in character. So I think this was clearly a mucocele of the large bowel resulting from multiple foci of obstruction.

DR MIXTER: Was there any true calcification?

DR MALLORY: We were not able to identify the calcification.

bell in shape Pancreatic cysts and liver cysts, particularly pancreatic cysts, may form calcareous deposits, but one would expect fullness in the epigastrium, certainly that is true of simple cysts of the liver I have seen one simple cyst of the liver that presented as a definite epigastric mass, which descended on respiration, and it would not fit into this category It is true that Meckel's diverticulum can attain enormous size, but it is not palpable except when it is accompanied by acute inflammatory reaction or perforates and forms an abscess So there again I think we can rule that out Let us now consider tumors that may be associated more commonly with calcification First let us consider calcified mesenteric glands Here we have, however, central foci that do not show a crescentic linear type of calcification that we see here Furthermore, a gland of this size would certainly be unusual Perhaps we should mention lithopedium, although the x-ray appearance would be different, and I think that is a far-fetched possibility We have to consider echinococcal cyst, a wandering cyst might be located in this region It is not uncommon to get a linear calcification, and this woman was an Italian There is no record of a complement-fixation test available

Hematomas may show calcification — although the calcification is usually more or less fuzzy and diffuse rather than linear

A gallstone may be palpable, and I have here one that I removed some years ago It is an interesting specimen and was readily palpable I could move it about the abdomen It made a perfect cast of the gall bladder In the case under discussion one would have to suppose that it had ulcerated through the gall bladder, wrapped itself in the omentum and worked its way down to the umbilicus The calcium deposit on the surface could well follow this type of shadow I think that is far fetched Calcification is frequently associated with any form of chronic abscess or infection

One thing we must consider is a pocket in the old ulcerative colitis that she had years previously, with a chronic abscess as well as calcification We cannot rule it out We have to consider other likely diagnoses

I do not believe this was a foreign body lying within the intestinal lumen It is true the human being is capable of all sorts of aberrations, and any cavity within the body may be a suitable receptacle for a foreign body Some of us have seen hairpins

introduced into the female bladder, and I have taken a rivet out of the male bladder But a foreign body introduced through an ileostomy would probably not stay in the intestine for nearly two years without either being extruded or causing difficulty On the other hand this patient was operated on twenty-three years before this admission I do not know what the sponge-count report was, but one of the things I have strongly in mind is that she had a sponge wrapped up in the omentum that caused this linear calcification such as we see in this film Sponges can lie quiescent for years I have removed one that was a movable mass in the abdomen, in a woman who had had an ovarian cyst removed some three or four years before The sponge had rolled itself up in the omentum and lay dormant over that period A sponge can show calcification of this type

Another calcified tumor that we must consider is uterine fibroid, pedunculated, or one that from torsion had separated by necrosis and then become engrafted at some other site, perhaps near the umbilicus Such tumors may show calcification of this type Another definite possibility is a pedunculated ovarian cyst, because ovarian cysts are prone to show a fine linear calcification I think I am right on that from the x-ray standpoint.

DR WYMAN Sometimes

DR MIXTER Particularly the dermoids have calcification that might follow this pattern

Time is drawing to a close and I must end my discussion, but I would say that there are three diagnoses I would particularly like to consider as possibilities I do not believe I would want to commit myself any further than that On the law of chances I would say first that this might be a foreign-body cyst, second, a dermoid, and third, a fibroid I believe the time is up, and as the old saying goes you never can tell what is in the box before you take the cover off I would like to know what operation showed

DR MALLORY Dr Warren, will you tell us your opinion and operative findings

DR RICHARD WARREN Our reasoning was not so astute as Dr Mixer's We had however more information that I am afraid did not get into the record There were two or three points that swayed us The first was that the patient had not had any passage of material by rectum for several years The record states that there was mucus passed every few months but that was inaccurate The

second point was that rectal examination was impossible because there was a complete block at the internal sphincter. Tying these facts together with the mass that was palpable in the region of the umbilicus we began to think this was inspissated material — accumulated colonic secretions. We could not explain the calcification. That bothered us a great deal.

CLINICAL DIAGNOSIS

Inspissated material in colon

DR MIXTER'S DIAGNOSIS

Cyst, due to foreign body

ANATOMICAL DIAGNOSIS

Mucocele of large bowel due to strictures in ulcerative colitis of defunctioned bowel

PATHOLOGICAL DISCUSSION

DR WARREN: We operated on the patient and found that she did have a greatly distended right colon — greatly distended with a mucoid type of material. The defunctioned terminal ileum was also distended to the same diameter as the colon. The material was under such tension that it was oozing out through the interstitial spaces. Most of it was in the right colon, although there were patches on the left side as far down as the lower segment. This material was incarcerated in several

compartments. The lumen of the colon at the rectal end was closed off as it was at the defunctioned end of the double-barreled ileostomy. It was interesting also that the patient had had acriflavine colonic irrigation for a year or so following ileostomy.

DR MIXTER: I am surprised there was not a palpable, putty-like mass in the right side of the abdomen.

DR MALLORY: This picture shows the entire colon here and the terminal portion of the ileum, which, as one can see, is dilated almost to the size of the colon. The next picture shows the bowel after it was opened, and here is one of these huge masses of inspissated secretion. As one passes along to the sigmoid there is another mass of mucus, not quite so large. The mucus, as Dr Warren said, had partially split the wall of the bowel so that we found mucus all through the layers of intestinal wall. This caused us considerable worry at first for fear we were dealing with colloid carcinoma, in which tumor cells may be very infrequent and one finds only great masses of mucus. Here and there, however, we could find remnants of intestinal epithelium, which were quite normal — not neoplastic in character. So I think this was clearly a mucocele of the large bowel resulting from multiple foci of obstruction.

DR MIXTER: Was there any true calcification?

DR MALLORY: We were not able to identify the calcification.

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PUBLIC HEALTH AND MENTAL HEALTH

MYSTERY and abstruseness continue to be associated with psychiatry and psychotherapy by people who know little about the subjects and by some who professedly know much about them. It is questionable whether the encouraging of awesome respect for this branch of medicine will do much toward advancing it on a sound basis.

An instance of comparative simplicity in concept and in teaching some of the principles of psychiatry is presented in a recently published pamphlet.* This pamphlet is the report on "An Institute on Mental Health in Public Health" held by the California State Department of Public Health and The

Commonwealth Fund last July. The Institute was attended by 27 health officers, and the teaching and discussion were conducted by 8 psychiatrists, 3 pediatricians with psychiatric training and 5 public-health leaders.

With the new impetus being given to the psychiatric implications in almost all human pursuits, it is understandable that the sphere of public health should be included in psychiatry's ambit. According to the pamphlet — a more comprehensive account is to be issued later — the Institute touched on many topics in its clinics, lectures and discussions, but its chief work and accomplishment was an inquiry into the understanding of "interpersonal relationships."

Health officers and health departments deal primarily with the prevention, amelioration and cure of disease. Concentration on the pathologic process is apparently the principal concern. The individual, with his particular personality, who has or may acquire the disease is considered secondarily or perhaps not at all. The Institute, in its daily meetings, revealed to its student members that it is people who have diseases, people with their fears, resentments, social, economic and emotional problems. It is an old story — the best care of the patient is care for the patient. Also, it seemed to become clear or clearer to the students that their own attitudes and personality problems could too frequently produce blind spots in their associations with other human beings, both patients and colleagues.

The pamphlet states "unless the health officer listens to the patient he cannot learn enough about the patient to know how to deal with him skillfully, and unless the health worker enters into a feeling relationship with the patient his advice and his questions are both likely to be fruitless." This is such a simple and apparently uninspiring conclusion that it may seem surprising and even disturbing that supposedly mature, intelligent public-health officers were pleased and delighted with the course.

It may well be that the students benefited from the opportunity to listen to and to discuss points and subjects that are relevant to what makes everyone tick. The "what," as described in the pamphlet,

*Smith, G. *Human Relationships in Public Health. Report of institute on mental health in public health* 18 pp. New York: The Commonwealth Fund 1949.

was not founded on disputable and unproved Freudian and neo-Freudian dogmas. That credits the teachers with perspective and wisdom.

Science will do better than it has to date if it proves anything more fundamentally constructive than the Golden Rule. A tip to science might be to extirpate self-interest in man without destroying or nullifying his constructive, altruistic energies.

AMERICAN BOARD OF PREVENTIVE MEDICINE AND PUBLIC HEALTH, INC

THE establishment of the American Board of Preventive Medicine and Public Health represents a significant step in medical progress. The Board, which is sponsored by the American Medical Association, American Public Health Association, Association of Schools of Public Health, Southern Medical Association and Canadian Public Health Association, has adopted requirements for certification that are in harmony with those of the various specialty boards previously set up. General qualifications, such as satisfactory moral and ethical standing in the medical profession, adequate medical training and internship in an approved hospital, and licensure to practice medicine in the United States. To be eligible for examination, applicants must also have had special training and experience in preventive medicine and public health for at least six years after internship (special academic training, or its equivalent, and field training or residency of at least two years of field experience in general public-health practice, including planned instruction, observation and active participation in a comprehensive, organized public-health program), each person to whom a certificate is issued must limit himself to the teaching or practice of public health as a specialty. Provision is made for the certification, without examination, of the Founders Group, consisting of practitioners of preventive medicine and public health who have achieved unquestioned eminence either in an academic status or through practical achievement in positions of responsibility. The standards thus set up appear to guarantee that diplomates of the new board will be men of the highest caliber in their field.

The newly recognized specialty is a matter of great interest to all physicians, since it is, in essence, the medical profession's answer to the challenge of providing adequate medical care on two crucial levels of medical practice. The setting up of the Board may be regarded as a forward step toward the goal of giving to every person "the basic essentials, diagnostic, preventive and therapeutic measures that will enable him to enjoy a more productive life and become a greater asset to the community."* The significance of progress in this vital field, which has for years been the battleground between the proponents of free practice and those who demand state control is obvious.

*Getting V A Public health today and tomorrow in Massachusetts
 McEneaney J Med 239 295 298 1948

NEW DIRECTOR OF MASSACHUSETTS GENERAL HOSPITAL

IN THE selection of a director to succeed Dr Nathaniel W. Faxon, who is retiring after twenty years of distinguished service, the trustees of the Massachusetts General Hospital have again demonstrated the excellent judgment that usually characterizes their decisions.

Dr Dean A. Clark, who will shortly assume the directorship of the hospital, is a native of Minnesota, a graduate of Princeton University and holder of the degrees of bachelor of arts and bachelor of science in physiology from Oxford University, where he studied three years as a Rhodes Scholar. He received his medical degree from The Johns Hopkins University School of Medicine in 1932, after which he served an internship in medicine at the Johns Hopkins Hospital. He then became assistant resident in medicine and neurology at the New York Hospital, National Research Council fellow in neurophysiology at the Cornell University Medical College, intern at Phipps Psychiatric Clinic, in Baltimore, and intern at Trudeau Sanatorium, in Trudeau, New York.

In 1938 and 1939 Dr Clark made a survey of group medical practice and medical service prepayment plans in various parts of the country. In the latter year he became a commissioned officer in the reserve corps of the United States Public Health Service, and for the next several years was en-

gaged largely in studies of the organization and administration of medical care programs. From 1941 through 1948 Dr. Clark also lectured or conducted courses on medical economics and the distribution of medical care in several colleges and universities. He is at present associate professor of public-health practice at Columbia University College of Physicians and Surgeons and lecturer in medical economics at the School of Public Health of the Uni-



DEAN A. CLARK, M.D., B.Sc. (Oxon)

versity of California. Since August, 1945, Dr. Clark has been on leave of absence from the Public Health Service devoting his time to the medical direction of the Health Insurance Plan of Greater New York.

Dr. Clark obviously brings to this important post a wide experience and unquestioned talent in medical organization and administration. In these times when new and better ways are being sought through which to deploy the services of medicine, expert guidance is needed in every area. The Massachusetts General Hospital is to be congratulated on having found such an able successor to its long line of illustrious administrators.

BIOLOGIC ENIGMA

MANY mysteries of the animal kingdom, according to a feature story released by the University of Wisconsin News Service, remain unsolved, although ardent naturalists have spent years in their investigation.

Thus it is not known why the Scandinavian lemmings make their periodic marches into the sea, why ocean salmon return to their home streams to spawn, nor, parenthetically, why the north Atlantic whale, with thousands of miles in which to roam, picks Cape Cod, Massachusetts, as a place to drive himself irreversibly ashore. The residents of that famous resort would like to know.

The Wisconsin scientists, intrigued by these biologic enigmas, have turned their attention to the migratory habits of bats, with particular reference to the locations that they select for their winter hibernation. Banding expeditions have been conducted in the abandoned mines, the caves and deserted houses of northern Wisconsin, but the bats discovered have been far fewer than those known to inhabit the region in the summer, and have been mostly males. When the search is extended, the belfries of the countryside will not be overlooked.

In the summer, females are discovered in great numbers in the local attics, where they bear (perhaps in place of gifts) their young. Apparently the hibernating males, despite their bachelor habits, have found an answer to the question (a sign of good breeding), "Shall we join the ladies?"

More light is shed on the same problem by the discovery that bats may be divided into two types: the social, who hibernate in colonies and presumably join the ladies, and the nonsocial, — the Chiropterous counterparts of the lone wolf and the bank beaver, — who, shunning the stag lines, are rarely found in groups and may migrate to distant climes in winter.

Perhaps the work with banding, Wisconsin News Service volunteers, will solve this mystery of the missing bats.

NOTES FROM THE MEDICAL EXAMINER

DEATH DUE TO CONFLAGRATION

Approximately 10,000 deaths per year in the United States are caused by burning or by other lethal attributes of conflagrations. In almost a quarter of these the victim is found dead at the scene of the fire. Such deaths are investigated by the medical examiner or coroner. Although the majority are due to the fire and are accidental, this is not invariably the case. Willful destruction of a dead body by fire may be an attempt to perpetrate an insurance fraud or to conceal a homicide. It is the purpose of this communication to review briefly the effects of conflagrations that are most frequently responsible for death on the premises and to discuss certain post-mortem characteristics of burned bodies that are likely to be of medico-legal importance.

One or several factors may be responsible for death during and because of a conflagration. Usually, smoke is inhaled before there is significant exposure to heat, and frequently the victim is unconscious or dead before there has been burning of the skin.

Although the composition of smoke varies enormously according to the type of fuel, the amount of oxygen available to support combustion, the temperature attained, and the extent to which the smoke has been diluted with air it almost invariably contains a dangerous amount of carbon monoxide. In a smoke-filled room the concentration of this gas is often so great as to cause loss of consciousness within a few minutes. In the case of smoldering fires dangerously high concentrations of carbon monoxide may be present in air that has so little visible smoke that it is erroneously regarded as safe to breathe. Even though the amount of carbon monoxide is not excessive carbon dioxide may be present in a concentration high enough to cause rapidly fatal asphyxia. Rarely is the oxygen content of smoke so low as to result in oxygen starvation.

If neither the carbon monoxide nor the carbon dioxide content of the smoke is high enough to cause asphyxia, various irritating combustion products may cause suffocation owing to rapidly developing edema of the air passages or lungs. Irritants contained in smoke derived from organic materials likely to be burned in an ordinary fire include acetic acid, aldehydes, ammonia, formic acid, furfural, pyroigneous acids, resins, saturated and unsaturated hydrocarbons and tar. Superheating of fats and certain oils causes the formation of highly toxic acrolein. Hydrogen cyanide and sulfide are both liberated in large amounts in the burning of wool. Highly irritating anhydrides of nitrogen are generated by the burning of various plastic and synthetic nitrocellulose compounds. All these

combustion products are injurious to the respiratory membranes and are capable of causing rapidly obstructive edema.

Failure to find evidence of smoke inhalation in the body of a person found dead at the site of a conflagration should lead to the suspicion that death occurred before the fire started. If the victim was alive and breathed smoke, carbon is usually present in the medium and small bronchi in amounts sufficient to cause a gray or gray-black discoloration. Usually, chemical irritants in the smoke cause an outpouring of mucus and the development of an intense hyperemia of the mucous membranes. As a rule the carbon monoxide content of the blood is significantly elevated.

It is true that some of the victims who die at the site of a conflagration do so because of burning when circumstances are such that fatal burning takes place before sufficient smoke has been inhaled to cause asphyxia or unconsciousness. Extensive and severe burning of the surface of the body may result in rapidly fatal circulatory failure because of peripheral vascular collapse and shock. If the victim is sufficiently close to flame to receive burns of the face the inhalation of heat may cause thermal injury of the larynx, with fatal laryngeal edema.

It is sometimes desirable to appraise cutaneous burns in terms of whether they were received before or after death. Fluid-filled blisters in association with cutaneous burning indicate vital reaction, unless putrefaction has started. If putrefaction has begun vesication may be a post-mortem artifact. Another artifact frequently encountered is the steam blister. When skin is superheated, whether it is live or dead, sufficient steam may be generated beneath an intact epidermis to cause it to become elevated. Such blisters either rupture immediately or collapse as soon as the skin cools and never contain fluid. The finding of a zone of edema and hyperemia at the junction of burned and unburned tissue is evidence of vital reaction. Although recognition of vital reaction establishes the fact that burning occurred during life, its absence does not necessarily exclude the possibility of ante-mortem thermal injury. Burning that began before death may be completely obscured by the continued application of heat after death.

The continued application of heat after death may cause the skin to contract and split with the formation of deep fissures that to the inexperienced observer resemble knife wounds. Protracted exposure of the dead body to intense heat causes the extremities to flex and to assume curiously distorted attitudes. The bones of a badly burned body become so brittle that they can be broken by the stream of water from a fire hose or in the removal of the body from the place of the fire. If the neck is badly burned the laryngeal cartilages often warp in such a manner as to occlude the airway. The hyoid bone may become so fragile as to break on manipulation.

Expansion of the intracranial contents by heat may cause the cranial sutures to separate and the calvarium to fracture in an explosive manner. Such thermal changes in the skull are often accompanied by massive epidural extravasation of blood from the great venous sinuses. Unless there is unmistakable external evidence of violence to the head the diagnosis of ante-mortem head injury in a case of a badly burned body should be made with great caution. The finding of subdural or subarachnoid bleeding or cerebral contusion or laceration may be prerequisite to recognition that skull fracture was probably ante mortem and due to physical violence rather than to heat.

No matter how badly burned the body, an adequate post-mortem examination may provide information to identify the dead person, to determine the time of death in relation to that of the fire and to establish the cause and manner of death. The physical characteristics of the body may not be consistent with those of the person it is supposed to represent. Death may have resulted from some other cause before the fire. It may be found that the decedent perished by fire because he was incapacitated by antecedent disease, injury or intoxication.

ALAN R. MORITZ, M.D.
Professor of Legal Medicine
 Harvard Medical School

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

PROGRAM FOR PREMATURE INFANTS

The program for the care of premature infants, established by the Division of Maternal and Child Health of the Massachusetts Department of Public Health in 1937-1938, was the first state program in the United States. At that time state-wide publicity was provided. During the ensuing years there have been many changes in local medical, nursing and board-of-health personnel so that it seems advisable again to outline the program in order that all concerned with the care of the premature infant may be cognizant of the facilities available for their care.

At the beginning of the program 48 hospital centers outside Boston adequately equipped to care for premature infants were established on a geographic basis so that infants born outside these centers would have a relatively short distance to travel for care.

Since then the licensing of hospitals has come into the Department of Public Health, with resulting improvement in standards of nursery care in many hospitals having maternity service other than the original centers. There are also in the city of Boston several hospitals equipped for care of premature infants brought in from outside areas.

In 1937 and 1939 legislation was passed allowing for transportation, if requested by physician and parent by the local boards of health, to hospitals equipped for care and for payment of reasonable hospital expenses of such infants by local boards of welfare when parents need such help without the parents' being deemed on public relief.

To facilitate these services the physician delivering the premature infant in the home is required by law to report such a delivery by telephone as soon as possible, and also in writing within twenty-four hours to the local boards of health and welfare. For premature infants born in the hospital the hospital superintendent is responsible for reporting to the local board of welfare of the town where the infant was born. The board of welfare of the town of settlement will reimburse the board of welfare of the town where the infant was born for hospitalization, provided the expense is incurred within ten days prior to the notice.

Thus, Massachusetts has made provision for reporting of all premature births, for transportation and for payment for hospitalization of the premature infant, and a group of hospitals is equipped to give adequate care.

The facilities for transportation and hospitalization appear to be the factors in the program that are least well known by physicians. It is thus the purpose to endeavor to bring these to the attention of the readers of the *Journal*. A number of hospitals have transportation facilities in the form of heated ambulances and baskets or cases for carrying premature infants that will keep the baby warm in transit. It is suggested that physicians make inquiries of the hospital, board of health or visiting-nurse association in the towns in which they practice regarding the methods of obtaining this service in emergency. It is further suggested and even urged that the premature infant be transported to the nearest hospital adequately equipped for care instead of being subjected to a long journey to a distant center. This may prevent infant deaths. It would be advisable to telephone to the hospital of choice in advance to ensure admission of the patient and to obtain any transportation facilities that the hospital is able to provide.

In 1947 a series of regional institutes for hospital administrators were conducted for the discussion of hospital nursing standards. Standards for care of the premature infant were included.

Before the war a refresher course was provided for all nursery supervisors in the hospital centers. Changes in personnel have occurred, and refresher courses are now being given again to new nursery supervisors, 26 nursery supervisors will have completed this course by July 1. It is planned to continue these courses until all are accommodated.

In communities where public-health nursing service in the field of infant-health supervision is available, help can be given to the mother after the

infant leaves the hospital Under the supervision of the physician the public-health nurse will help the mother to prepare for the baby's homecoming She will also demonstrate bathing and other care recommended by the physician and will make periodic visits to the home and progress reports to the physician This is a good preventive health measure and also gives the mother confidence in caring for her baby When such assistance is desired the physician or the hospital should notify the public-health nurse of the date of discharge as far in advance as possible

FLORENCE L MCKAY, M D
Director, Division of Maternal and Child Health

DIRECTIONS FOR IMMEDIATE CARE OF PREMATURE INFANTS

The Massachusetts physician who delivers a premature infant in one of the approved hospitals listed in Table 1 will have full physical and nursing

TABLE 1 *Hospital Centers for the Care of Premature Infants with Equipment and Routines Approved by the Massachusetts Department of Public Health*

LOCATION	HOSPITAL
Southeastern District	
Attleboro	Sturdy Memorial Hospital
Fall River	Truesdale Hospital
Barnstable	St. Anne's Hospital
Nantucket	Cape Cod Hospital
New Bedford	Nantucket Hospital
Oak Bluffs	St. Luke's Hospital
Taunton	Martha's Vineyard Hospital
	Morton Hospital
South Metropolitan District	
Frammingham	Frammingham Union Hospital
Quincy	Quincy City Hospital
Weymouth	South Shore Hospital
North Metropolitan District	
Cambridge	Mount Auburn Hospital
Malden	Malden Hospital
Newton	Newton-Wellesley Hospital
Waltham	Waltham Hospital
Northeastern District	
Beverly	Beverly Hospital
Haverhill	Haverhill Municipal Hospital
Lawrence	Lawrence General Hospital
Lynn	Lynn Hospital
Melrose	Melrose Hospital
Salem	Salem Hospital
	North Shore Babies Hospital
South Central District	
Worcester	Worcester City Hospital
	Worcester Memorial Hospital
	St. Vincent Hospital
North Central District	
Clinton	Clinton Hospital
Fitchburg	Burbank Hospital
Gardner	Henry Heywood Memorial Hospital
Leominster	Leominster Hospital
Lowell	Lowell General Hospital
	St. John's Hospital
Connecticut Valley District	
Greenfield	Franklin County Hospital
Holyoke	Holyoke Hospital
	Providence Hospital
Montague	Farren Memorial Hospital
Northampton	Cooley Dickinson Hospital
Springfield	Wesson Maternity Hospital
	Mercy Hospital
	Noble Hospital
Berkshire District	
Great Barrington	Fairview Hospital
North Adams	North Adams Hospital
Pittsfield	St. Luke's Hospital
	Pittsfield General Hospital

facilities at hand for the baby's care Should a physician be present at or called in after a premature delivery in another hospital or at the mother's home, his primary responsibilities are to

keep the infant under the best possible circumstances until it is admitted to an approved nursery, and to see that this admission is promptly accomplished

The immediate care of the infant should be largely a matter of ensuring warmth and protection from potential sources of infection The only word necessary regarding feeding is a warning against any attempts in that direction until the baby has been

TABLE 2 *Other Hospitals Equipped to Care for Premature Infants Brought in From the Outside*

LOCATION	HOSPITAL
South Metropolitan District	
Brockton	Goddard Hospital
	Brockton Hospital
North Metropolitan District	
Boston	Allerton Hospital
	Boston City Floating
	Boston Floating Hospital
	Carney Hospital
	Children's Medical Center — Infant's Hospital
	Faulkner Hospital
	Massachusetts General Hospital (Vincent Building)
	New England Hospital for Women and Children
	Santa Maria Hospital
Cambridge	Cambridge City Hospital
Concord	Emerson Hospital
Medford	Lawrence Memorial Hospital
Northeastern District	
Amesbury	Amesbury Hospital
Ipswich	Cab'e Memorial Hospital
Woburn	Charles Choate Memorial Hospital
South Central District	
Southbridge	Harrington Memorial Hospital
Worcester	Hahnemann Hospital
North Central District	
Lowell	St. Joseph's Hospital
Berkshire District	
Adams	Plunkett Memorial Hospital

placed under proper nursing care and environment, and even then a day or two without feeding is recommended

Warmth should be a matter of seeing that the body temperature does not fall after birth rather than of applying heat once the baby becomes cold Any covering that is clean, soft and prevents heat conduction is satisfactory A sterile towel, or, failing that, a clean towel, wrapped about the body and scalp, with several thicknesses of soft blanket wrapped over towel and infant, is ideal A hemostat may be left on the cord until a proper tie can be applied in the nursery to which the infant is sent Thus covered, the infant may be laid near a radiator or stove or in whatever warm area is available Serious burns may result from the hasty use of hot water bottles, which should not be needed if the procedures mentioned above are performed expeditiously

Protection from infection means, mainly, protection from people Speed in removal to a proper premature nursery will accomplish this and better than will any other activity It may here be stated that these infants have remarkable powers of survival for the first several hours after birth, so that it is usually not necessary that they be frequently unwrapped or otherwise disturbed for inspection

A list of hospitals with nurseries properly equipped and staffed for care of premature infants is presented in Table 2 It should be possible to trans-

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At the beginning of the program 48 hospital centers outside Boston adequately equipped to care for premature infants were established on a geographic basis so that infants born outside these centers would have a relatively short distance to travel for care.

Since then the licensing of hospitals has come into the Department of Public Health, with resulting improvement in standards of nursery care in many hospitals having maternity service other than the original centers. There are also in the city of Boston several hospitals equipped for care of premature infants brought in from outside areas.

In 1937 and 1939 legislation was passed allowing for transportation, if requested by physician and parent by the local boards of health, to hospitals equipped for care and for payment of reasonable hospital expenses of such infants by local boards of welfare when parents need such help without the parents' being deemed on public relief.

To facilitate these services the physician delivering the premature infant in the home is required by law to report such a delivery by telephone as soon as possible, and also in writing within twenty-four hours to the local boards of health and welfare. For premature infants born in the hospital the hospital superintendent is responsible for reporting to the local board of welfare of the town where the infant was born. The board of welfare of the town of settlement will reimburse the board of welfare of the town where the infant was born for hospitalization, provided the expense is incurred within ten days prior to the notice.

Thus, Massachusetts has made provision for reporting of all premature births, for transportation and for payment for hospitalization of the premature infant, and a group of hospitals is equipped to give adequate care.

The facilities for transportation and hospitalization appear to be the factors in the program that are least well known by physicians. It is thus the purpose to endeavor to bring these to the attention of the readers of the *Journal*. A number of hospitals have transportation facilities in the form of heated ambulances and baskets or cases for carrying premature infants that will keep the baby warm in transit. It is suggested that physicians make inquiries of the hospital, board of health or visiting-nurse association in the towns in which they practice regarding the methods of obtaining this service in emergency. It is further suggested and even urged that the premature infant be transported to the nearest hospital adequately equipped for care instead of being subjected to a long journey to a distant center. This may prevent infant deaths. It would be advisable to telephone to the hospital of choice in advance to ensure admission of the patient and to obtain any transportation facilities that the hospital is able to provide.

In 1947 a series of regional institutes for hospital administrators were conducted for the discussion of hospital nursing standards. Standards for care of the premature infant were included.

Before the war a refresher course was provided for all nursery supervisors in the hospital centers. Changes in personnel have occurred, and refresher courses are now being given again to new nursery supervisors, 26 nursery supervisors will have completed this course by July 1. It is planned to continue these courses until all are accommodated.

In communities where public-health nursing service in the field of infant-health supervision is available, help can be given to the mother after the

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ANNUAL ORATION

SOME RESPONSIBILITIES OF MEDICAL EDUCATION*

C SIDNEY BURWELL, M D †

BOSTON

TO DELIVER the Annual Oration of the Massachusetts Medical Society is an honorable privilege, for which I am grateful

For almost fourteen years, as dean of the Faculty of Medicine, I have had the chief responsibility for the administration of the Harvard Medical School. This experience is the reason for my choice of subject and presumably the basis of the Society's choice of an orator. The organization and progress of medical education have been my chief preoccupation for these fourteen years, and I welcome the opportunity to place on record my faith and my optimism regarding it. As I have contemplated medical schools in general and the Harvard Medical School in particular, I have been asking myself with special insistence what are these schools for, and what are they trying to accomplish? Even a general answer to these questions could be useful. In the next few weeks I shall leave the dean's office to return to teaching and research, hoping, as one may say, to regain my amateur standing, and so I speak with a particular sense of freedom and entirely for myself, not as a dean, but as a private citizen who has had some experience with these problems.

There are many reasons why it is pleasant to meet in Worcester. One is that it gives an opportunity to look at medical schools from a distance of some forty miles — a circumstance calculated to permit a view of the forest without being lost among the trees.

Members of the medical profession are not apt to consider the Army and the Navy as academic organizations, or to expect them to excel in educational enterprises. Nevertheless, some of the training programs of the armed forces during the war held lessons for formal educational organization. These training programs taught selected

young men to fly, to detect submarines, to carry a gun or to speak German in what seemed to many professional educators a surprisingly short period. If one seeks causes for the success of these programs, so far as they were successful, he is apt to conclude that one factor was that the organizers of these programs were able to define with great clarity and simplicity the program's objectives. They were able to say what knowledge, what skills, what habits of mind and muscle they wished the trainee to acquire, and they could eliminate with complete ruthlessness any material, any exercise, any point of view that did not contribute to these specific and limited ends. The organizers of these training programs were not concerned with general education or with a distant future, but with an immediate, limited and definable goal. Moreover, they were able to select their candidates freely and to weed them out without hesitation.

I should be the last to deny that there are many differences between Army or Navy or Air Force training and medical education, but I do submit that medical schools would have better organization and planning if there were clearer understanding and better agreement as to the objectives of the medical school program.

The responsibilities of medical schools, to my mind, may be summarized in six major categories:

PROVISION OF INSTRUCTION LEADING TO THE DEGREE OF DOCTOR OF MEDICINE

When the Harvard Medical School began its work one hundred and sixty-seven years ago, its faculty was mainly concerned with offering instruction to prepare men directly for practice. The faculty of today continues to accept as a primary responsibility the provision of instruction leading to the M D degree, a course that is still the basis of an informed and competent profession. As we approach a discussion of this first basic objective, the undergraduate course, we encounter the theme

*Presented at the annual meeting of the Massachusetts Medical Society, Worcester, May 24, 1949.

†Dean of the faculty of medicine and research professor of clinical medicine, Harvard University physician, Peter Bent Brigham Hospital.

port an infant born anywhere in Massachusetts to one of these hospitals within less than an hour. Most of them have, or have access to, an artificially heated carrier, which can be placed in any automobile and sent out as a "premature ambulance." Plans are now maturing for the provision, by a generous donor, of such an "ambulance" wherever a survey now in process demonstrates that one is clearly needed. Most of those in present use have a connection by which they can be converted into oxygen chambers by the attachment of a portable oxygen tank.

All the physician need do is to telephone the nearest approved hospital at once, give details and arrange a plan by which the ambulance may be sent out. This often means dispatching the infant's father or other relative in a car or taxicab. The hospital can be warming the ambulance until his arrival, and not only should send the ambulance and oxygen with him but also should provide a nurse or house-staff member to watch over infant, ambulance and oxygen on the return journey. Since we have occasionally seen infants arrive at our own hospitals in supposedly oxygenated carriers in which no one had bothered to turn on the oxygen tank, the doctor may well make sure that those accompanying the baby to the hospital know how to use their equipment. He should also see to it that a proper history, or a person able to give such a history, accompanies the infant.

A word may be added about vitamin K and stimulants. Nothing of importance will be lost if the former is not administered till the infant arrives at the nursery where he is to be cared for. Stimulants are seldom called for and, unless given by those familiar with the care of premature patients, might often better be avoided. If the infant's condition is rapidly failing and there is unavoidable delay in his admission to an approved nursery, caffeine sodium benzoate, $\frac{1}{4}$ gr (16 mg), may be given intramuscularly, and repeated once if no improvement has occurred at the end of fifteen minutes.

This section was prepared by the Massachusetts State Committee on the Fetus and Newborn of the American Academy of Pediatrics

DR W BRADFORD ADAMS, Springfield

DR FRED H ALLEN, Holyoke

DR JOSEPH GARLAND, Boston

DR PAUL J JAKMAUH, South Boston

DR ROBERT T MOULTON, Salem

DR ALFRED S O'CONNOR, Worcester

DR HERMAN C PETTERSON, Boston

DR STUART F STEVENSON, Boston

DR ALFRED WELLER, Arlington Heights

DR CLEMENT A SMITH, Boston

Chairman

BOOK RECEIVED

The receipt of the following book is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Autobiography of Benjamin Rush His "Travels Through Life" together with his Commonplace Book for 1789-1813
Edited with introduction and notes by George W Corner, M D, 8°, cloth, 399 pp., with 8 illustrations and frontispiece
Princeton, New Jersey: Princeton University, 1948 \$6.00

NOTICES

AMERICAN COLLEGE OF PHYSICIANS RESEARCH FELLOWSHIPS

The American College of Physicians announces that a limited number of fellowships in medicine will be available from July 1, 1950, to June 30, 1951. These fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in internal medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work. The stipend will be from \$2200 to \$3200.

Application forms will be supplied on request to the American College of Physicians, 4200 Pine Street, Philadelphia 4, Pennsylvania, and must be submitted in duplicate not later than October 1, 1949. Announcement of awards will be made in November, 1949.

(Notices concluded on page xvii)



When ordering needles cisternal,

Books, sponges or doses diurnal,

Dr Wise always mentions

(Or has those intentions)

The ads that he reads in the Journal

explosive expansion of knowledge in these areas and the growth of research in universities, institutes, hospitals, Government departments and industry create a demand for competent scientists in these fields that is simply not being met

Medical schools are now facing, more clearly than before, their share of responsibility for the basic training of these indispensable people. Adequate provision for training the successors to the present generation of such scientists is a part of the duty of universities and medical schools and one of the methods for expanding total medical personnel. Harvard University attempts to meet the problems by an ingenious collaboration between the pre-clinical departments of the Medical School, on the one hand, and the Faculty of Arts and Sciences on the other—a strong and useful combination called the Division of Medical Sciences. Before the war there were some 10 men a year in training as Ph.D. candidates in this division. This year there are 50—an example of a fivefold expansion of one part of the program of medical education. If medical schools do not accept their share of responsibility for training successors to the leaders of the medical sciences, teaching will suffer and the broad and expanding program of medical research will be restricted and injured.

ADVANCEMENT OF KNOWLEDGE BY RESEARCH

The advancement of knowledge is a fundamental university objective, and a major responsibility of medical schools. These schools are in a position of peculiar advantage, standing as they do between the science departments of the university on the one hand and the great teaching hospitals on the other. The research armies of a medical school can make their attack on a wide front and have the enormous advantages of diverse talents and an integrated program. Medical schools, in my opinion (by some considered a prejudiced one), have in the long run great advantages over other forms of organization for medical research, such as research institutes and hospitals. The special advantages of medical schools as research centers include the favoring presence of students and the possibility of a broad, well based spectrum of research running from the infrared of the bedside to the ultraviolet of the basic sciences in the university. It is my conviction that research is not only an opportunity but also a duty of medical schools and that its spirit and performance should be expected of each professor (in varying kind and degree) and of every department. I am equally concerned that teaching (of varying kind and degree) should be expected of every professor and every department. The integration, the mutual stimulation of teaching and research is the most healthful exercise undertaken by individuals or departments. There is no fundamental schism between research and teaching, or between different kinds of research.

In a recent valuable report of the "Medical Curriculum Committee of the British Medical Association" (under the distinguished chairmanship of Professor Henry Cohen of the University of Liverpool) the following wise sentences occur:

Claims of precedence or rivalry between clinician and laboratory researcher are falsely based and senseless, in Medicine, one cannot exist without the other, each must contribute his quota to the ultimate objective—the promotion of health, the relief of suffering and the elimination of disease in man. The scientific outlook and the humane approach in Medicine are complementary.

Research as an essential function of medical schools needs no defense: it advances knowledge, it helps all teaching, and it is indispensable to advanced training.

No one is going to quarrel very violently with the ideas expressed that training for the M.D. degree, training for the Ph.D. degree in medical sciences and research over a wide front are primary and pressing objectives of medical schools. Controversy, uncertainty and lack of knowledge are much more apparent when we come to consider the next objective.

PROVISION OF OPPORTUNITY FOR ADVANCED TRAINING FOR PRACTICE, TEACHING AND RESEARCH

What are the varieties of advanced training that may concern medical schools? Let me illustrate by describing the situation as I see it in the Harvard Medical School at the moment. There are at least three groups of individuals to whose advanced training the medical school has some relation. First, there are about 175 students classified as research fellows. This long list includes doctors of medicine and doctors of philosophy in various medical sciences. They are learning by doing in the field of research and to some degree in the field of teaching. They participate in the work of research teams as a means of equipping themselves to do research on their own. It is from this kind of group that many of the teachers and investigators of the next generation will come. Medical schools clearly have a primary responsibility for providing opportunity to these men. It is a logical place for such work to be located because teachers and investigators in the medical sciences require experience in departments of medical sciences, and these exist, on the whole, in medical schools. It is equally important, to my mind, that the growth of investigators in clinical fields should also be centralized in medical schools because I believe that the evidence of the last twenty years indicates that the clinical investigators of this generation are not able, by themselves, to train the clinical investigators of the next generation, but that the evolution of these investigators, if they are to be effective, requires the help of medical-science departments of medical schools.

The second group is also a large one, less precisely related to the medical school, but clearly influenced

of this address, if it can be said to have one. That theme is as follows: a characteristic of twentieth-century medicine is *rapid change* in knowledge and in practice.

In David McCord's* anthology of light verse, there is a composition by Mr. Newman Levy that concerns the characteristically rapid change of modern life. It is entitled "I Wonder What Became of Rand, McNally," and the most relevant verses run thus:

Mr. Rand and Mr. McNally,
Arbiters of hill and valley,
Portraitists of sea and land,
Mr. McNally and Mr. Rand
Two sad cartographic chaps,
Sat in their office surrounded by maps,
Globes and maps around the room,
And on *their* maps a look of gloom.

"Time was when this business of ours was grand,"
Said Mr. McNally to Mr. Rand,
"When our toughest job was to sit and think
Shall France be purple and Britain pink?
Shall Spain be tinted a bright cerise,
And perhaps a dash of green for Greece?"

"But that," said Rand to Mr. McNally,
"Was before Benito got rough with Hallie,
When we didn't fret about changing borders,
And we just sat here receiving orders."

"Remember those days," McNally said,
"When we'd plan a map a month ahead,
And we'd know, if it came out at noon, let's say,
It was up to date the entire day?"

"Those days," said Rand, "are gone *totally*."
"You said it, brother," said Mr. McNally.

The changes of the recent past have multiplied the variety of careers in medicine. Those equipped with medical training may translate it into the practice of surgery or of psychiatry, into general practice or that of ophthalmology. They may go into research and work with methods as diverse as those of nuclear physics, of statistics and of psychoanalysis. They may go into teaching, or into hospital or medical-school administration. The basic course, then, must *be* a basic course, not aimed simply or singly at preparing men for any one of these careers, but qualified to serve as a foundation for all. It must do better than this, it must serve as a foundation for types of careers that are still unknown but that will surely evolve in the years ahead.

A suitable plan of instruction, in a changing world, is concerned with developing in students not only knowledge of facts, not only good ways of using facts, but in particular, and at all possible times, providing a basis for understanding facts. Medicine should be taught, so far as our knowledge permits, in terms of the mechanisms of the phenomena of health and disease, thinking all the time about "why" and seeking always (to borrow a phrase from that rich source of memorable phrases, Mr.

*McCord D. T. W. *What Cheer: An anthology of American and British humorous and witty verse gathered, sifted and salted*. 515 pp. New York: Coward-McCann Inc., 1945.

Winston Churchill) "the unique and inexorable sequence of cause and effect."

Teaching based on this principle is often successful and stimulating, one is tempted to think that emphasis on mechanisms and sequences is perhaps the chief merit of modern medical education. There is another point in favor of this philosophy. If one believes that a chief function of what we may agree to call undergraduate medical education is to establish a basis for the continuing self-education of graduates, then emphasis on understanding is of central importance. The war was a testing ground for men and for methods of education. Many colleagues, on the basis of their war experience, have brought forcibly to my attention two attributes of the young physicians who during the war were best able to adapt themselves to unfamiliar varieties of medical activity. Let us remember that these unfamiliar varieties of medical activity were carried on under unfamiliar and difficult circumstances and by unfamiliar methods. These attributes of professional success were, first, stability and integrity of character, and, second, a good basic understanding of disease in terms of pathology, physiology, immunology, psychobiology and the other general formulations that underlie our understanding of the interactions of man and his complex and changing environment. Such attributes permit a young man to adjust himself to the unfamiliar tasks of military medicine and permit him to adapt himself to and utilize the changes brought about by the advance of knowledge.

I conclude that a major objective of medical schools is to provide the M.D. candidate with educational opportunity planned to let him acquire an understanding of the mechanism and the natural history of man and his diseases. The degree is not a certification of fitness for practice, it is a certification of basic medical training—the decision of readiness for practice is another. In the United States the several states reserve to themselves the right to say when a physician is ready and suitable to practice his profession.

So much for this indispensable objective and duty of medical schools in training physicians for participation in the medicine of the future by the provision of instruction leading to the ancient and worthy degree of Doctor of Medicine.

PROVISION OF INSTRUCTION LEADING TO THE DEGREE OF DOCTOR OF PHILOSOPHY IN ONE OF THE MEDICAL SCIENCES

There is an over-all shortage of physicians. This assertion is the subject of general agreement although no two people are agreed about the degree of the shortage. But, however severe this shortage is, there is another shortage even more severe: that of teachers and investigators in the fields of the "medical" sciences such as physiology, biochemistry, pharmacology, pathology and bacteriology. The

We may ask ourselves, "What is the essence of his plan of graduate education?" It is, I think, quite simple. First, he assumed the responsibility for planning and carrying out the program of his own continuing education. Second, he defined his goal. He drew the specifications of the kind of life he wished to have and the kind of doctor he wished to be. Third, he systematically, patiently and industriously acquired the skills, the knowledge, the judgment based on experience that made it possible for him to be that kind of doctor. In general, that is the way I think advanced training should be managed, with a minimum of specification from schools or boards and with a maximum of individual responsibility.

PARTICIPATION IN COMMUNITY SERVICES, IN THE PROVISION OF MEDICAL CARE, PREVENTION OF DISEASE AND EDUCATION OF THE PUBLIC

The medical school as compared with other parts of universities stands in a special relation to the larger community. An important part of the teaching in the medical school is carried on by university appointees working in hospitals and by the participation of both teachers and students in the actual work of community service institutions, such as hospitals. As a part of its university function, therefore, the medical school actually takes part in the provision of community service. In the provision of such service, university personnel and university organization have certain special obligations. One is to see that the community services in which the university participates attain a quality that the university is willing to see accepted as an example of standards of performance that medical students may follow. In medical care, for example, medical-school teachers must set an example not only of technical competence but also of humanity, of the treatment of the whole person, of the utilization of community resources, of the recognition of environmental factors and of all the varieties of professional responsibility. When such an example is set, the medical school is serving the cause of education, is assisting the hospitals and is helping the community.

RECRUITMENT AND SELECTION OF MEDICAL PERSONNEL

So far we have considered the objectives of the medical school as they relate to the basic instruction of prospective physicians, leaders in the medical sciences, teachers and investigators, the responsibilities of the medical schools as centers for the creation of new knowledge and its relation to community activity. There is another responsibility that needs to be discussed and that in some ways is fundamental to all the rest. It is this: in general, medical schools are responsible for the *recruitment* and *selection* of the individuals who will make up the medical profession of the next generation. They

play the role of the guardians of the gate, of St. Peter or of Cerberus, according to one's point of view. Obviously, the quality of the group so admitted to the profession depends upon two major factors: first, what individuals apply to medical schools for admission, and, second, what individuals are selected from the applying group?

In the past, most of the thought and time of faculties of medical schools have been concerned with the matter of selection. Perhaps it is now time for the faculties, and indeed for the medical profession, to give consideration to the still broader problem of the factors that attract men to the profession of medicine and those that repel them. These recruitment factors are partly the responsibility of medical schools and partly that of the profession at large. The factors that attract men to medicine include such diverse influences as their interest in science or in human beings, the tradition of their families, the romantic attraction of the profession, the prestige of medicine and its opportunities for service, for research and for a life of dignity and community standing. The factors that repel men from medicine include the cost of education, the ever-increasing prolongation of the training and the uncertainty of the future. It is not always recognized that in a changing world the professions that have a long training period are apt to be at a disadvantage so far as recruitment is concerned because it is so difficult to prophesy what the state of the profession will be when the long training has been achieved. At any rate, a systematic study of the factors that lead men to enter or to refrain from entering medicine is an important job for someone to do in the future.

Selection is a perennial problem. No one is satisfied with the methods, and no experienced person is prepared to suggest the ideal procedure. What is sought here, since we are talking about objectives, is a student body made up of individuals who have the intellectual capacity to deal with the prodigiously complicated and a rapidly changing period of medicine, who have the integrity and moral strength that we call character, and who represent wide varieties of talent and interest so that they can play successful roles in the extraordinarily diverse parts of the medical spectrum. To end up with a superior profession requires a wide variety of superior applicants, skillful admission committees, and *freedom to select the best men*.

The recognition of intellectual superiority is easier by formal tests than judgment of character. So far, selection by formula has not been as successful as a combination of statistical material with the judgment of experienced teachers. As has been repeatedly emphasized, they are being selected for general practice, for highly technical specialties such as ophthalmology, for surgery, for psychiatry, for research in fields as diverse as nuclear physics and the unconscious mind, for teaching, for administration, for careers in the sciences underlying medi-

by many members of its faculty. This is the group receiving advanced training for practice, including house officers in the hospitals in which Harvard Medical School teaching is done, and also those who attend the so-called "courses for graduates." This is the field in which the least clarity regarding the role of the medical school exists. Obviously, medical schools cannot be responsible for all or even a large part of advanced training for practice, so that this is peculiarly an area in which definition of objectives and roles of different organizations is urgently needed.

The situation is made more of an emergency by the rapid development of specialty boards and the expansion of their requirements. To my mind, a particular danger threatens advanced training of these types. It is in danger of becoming stereotyped by over-organization, and so becoming preparation for the medicine of today or even yesterday, rather than for the medicine of tomorrow. This danger threatens M.D.'s (in training for practice, teaching and research in medicine) more than it does Ph.D.'s (in training for similar work in the medical sciences).

A point of view relating to this problem may be described in terms of the following case history.

Among the figures that stand out in the great army of men who have contributed to our knowledge of heart disease is the slender silhouette of James Hope. James Hope was born at Stockport in the county of Cheshire, England, on February 23, 1801. The grammar school at Macclesfield having given him what it could, he determined on a career in the law. Before he embarked on this course, however, he went into the Yeomanry Lancers (at the age of eighteen) and spent a year in military service, or something approaching it. At the age of nineteen he began the study of medicine at the University of Edinburgh. His medical-school career was somewhat irregular, since he left the school before the end of his final year to take an excellent hospital post that offered itself at that time. He took this job with the blessing of the faculty and returned in 1825 to present his thesis and to take his degree. At the time of his graduation, Hope was twenty-four years old, intelligent, able, ambitious and possessed in a high degree of a most valuable characteristic, the habit of effective and unremitting industry.

As a medical student he had paid particular attention to pathological anatomy and to pathological physiology, believing those subjects to be the basis of intelligent practice. He had developed a native talent for drawing to great facility in medical illustration and had already begun the collection of drawings of specimens obtained at autopsy that were to be used in his own books later on. He proposed as his own goal to be a highly competent internist, with special interest and skill in the field of cardiovascular disease, and he set out to train himself to be the kind of person he wanted to be.

First, he took a dressership at St. Bartholomew's Hospital because he was convinced by his own observations that medical people did not know enough about surgery. This was followed by a year in Paris in the exciting atmosphere of the great French clinical school. He reached Paris in 1826. Laennec had just died (of tuberculosis), but Chomel was professor of clinical medicine at La Charité, and working with him were Andral, Louis and other stimulating teachers. Hope spent a month acquiring facility in speaking and understanding French and then went to work in ward and autopsy room. He labored not only to learn and to understand but also to perfect himself in the newer technics of physical diagnosis. No doubt some of his colleagues thought his diligence wasted, since many of these technics were so new that there was no general agreement about their future importance in the practice of medicine. After this year of rich clinical experience in France, he worked systematically for another year in the hospitals of Italy, Bavaria and Holland. At twenty-seven he was, as he had set out to be, a well trained internist with a broad clinical experience and with a special competence in the field of his interest. He knew the literature, he knew the men, he knew the subject. He was skilled in the technical aspects of the field and had had some exposure to the methods of thought and the methods of procedure of experimental medicine. He began his practice. At thirty he published a treatise entitled "The Diseases of the Heart and Great Vessels"—a book that Dr. Herrick, in his short *History of Cardiology*, says, "Outclassed all other books on the subject that had then been published." Dr. Herrick goes on to say further:

Hope struck a new note in the literature of heart disease. His volume has a modern ring to it. His discussion of the anatomy and physiology of the heart, heart murmurs and other physical signs is thorough and scientific with conclusions drawn from a study of the writings of others, as well as from his own experimental and clinical observations.

Hope's book had a deserved success. He influenced the practice of medicine in England, in Continental Europe and in America. My conclusion is that in spite of his untimely death from tuberculosis at the age of forty James Hope made important contributions to our knowledge of medicine and to its translation into practice. I do not suggest that he be taken as a complete model for young men in medicine. He was able and useful, but he had defects of character that made his ultimate stature less than it might otherwise have been. He was egocentric, jealous and hypersensitive, and neither generous nor fair in controversy. But in spite of these limitations of character it seems reasonable to conclude that his plan for the advanced training of James Hope was a successful one.

We may ask ourselves, "What is the essence of his plan of graduate education?" It is, I think, quite simple. First, he assumed the responsibility for planning and carrying out the program of his own continuing education. Second, he defined his goal. He drew the specifications of the kind of life he wished to have and the kind of doctor he wished to be. Third, he systematically, patiently and industriously acquired the skills, the knowledge, the judgment based on experience that made it possible for him to be that kind of doctor. In general, that is the way I think advanced training should be managed, with a minimum of specification from schools or boards and with a maximum of individual responsibility.

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The recognition of intellectual superiority is easier by formal tests than judgment of character. So far, selection by formula has not been as successful as a combination of statistical material with the judgment of experienced teachers. As has been repeatedly emphasized, they are being selected for general practice, for highly technical specialties such as ophthalmology, for surgery, for psychiatry, for research in fields as diverse as nuclear physics and the unconscious mind, for teaching, for administration, for careers in the sciences underlying medi-

cine and for fields of the future even the identity of which is as yet unknown. It is a nice assignment, and it does not lend itself to solution by a narrow formula.

William James said something to the effect that there is not much difference between one man and another, but that what difference there is turns out to be very important.

In summary, then, it appears that the objectives of medical schools include the following: the provision of instruction leading to the M.D. degree, the provision of instruction leading to the Ph.D. degree in medical sciences, the prosecution of research over a wide spectrum, the provision of ad-

vanced training for practice, for research and for teaching, participation in the community service of hospitals and other institutions of medical service, the recruitment and selection of the medical profession of the future.

* * *

In attacking these objectives, schools need the help, the support, the criticism and the understanding of the medical profession. It is a great and happy privilege to be able thus to present my concepts to this important part of our profession, the Massachusetts Medical Society.

THE EFFECT OF THE RICE DIET ON THE LEVEL OF THE BLOOD PRESSURE IN ESSENTIAL HYPERTENSION*

DOROTHEA G. LOOFBOUROW, M.D.,† ANNIE L. GALBRAITH, B.S.,‡ AND ROBERT STERLING PALMER, M.D.§

BOSTON

INTEREST in the influence of diet on the course of hypertension has existed for at least half a century. In 1904, in France, Ambard and Beaujard¹ advocated the use of a low-salt diet for the treatment of hypertension. In the early 1920's in this country Allen and Sherrill² and O'Hare and Walker³ reported on the use of low-salt diets in hypertension. These workers believed that the effect was produced by restriction of the chloride ion. Addison⁴ was among the first to suggest that the sodium ion was the important element, and came to the conclusion that "One has forced on one the concept that the prevalence of arterial hypertension on this continent (North America) is in large part due to potash poor diet and an excess use of salt (sodium chloride) as a condiment and preservative of meat." In 1920 Mosenthal⁵ discussed the influence of protein foods on the blood pressure, and concluded that restriction of this dietary component had little or no beneficial effect. In 1929 Berger and Fineberg⁶ reported on 13 patients on a low-sodium diet, stating that they failed to see any unquestioned blood-pressure modification that they could attribute to sodium restriction. Interest in the dietary treatment of hypertension lagged until 1944, when Kempner⁷ reported on the treatment of kidney disease and hypertensive vascular disease with the rice diet. Since that time there has been a renewal of interest. Many workers,⁸⁻¹¹ believing that the most important factor in the rice diet was the restriction of sodium chloride, have used a very low-sodium diet, which has otherwise met the accepted standards of adequacy in other food essentials (National Research Council

standards). Kempner's rice and fruit diet has been said to combine practically all the theories that have been advanced for the dietary treatment of hypertension, being low in sodium (200 mg), low in protein (20 to 25 gm), low in fat (5 gm) and restricting fluid intake to 800 to 1000 cc.

One naturally speculates about the rationale of using such a restrictive diet as Kempner's, which violates the accepted pattern of proper nutrition. Kempner¹² says, in a recent publication, "The treatment of hypertensive vascular disease with the rice diet was suggested by observations made on the protein, fat and carbohydrate metabolism of isolated kidney cells under various pathologic conditions (cell injury and/or changes in pH, sodium bicarbonate concentration, oxygen tension, and metabolizable substrate)." Working with damaged kidney tissue, he was led to consider the kidney as an organ of metabolism¹³ as well as an excretory organ. He postulated that pathologic conditions in the kidney lead to changes¹⁴ that may be summarized as follows: certain substances that are normally removed by kidney metabolism may be increased in amount, whereas other substances produced by the kidneys may be decreased in amount. These abnormal substances, which accumulate as a result of disturbed kidney metabolism, may be presumed to be harmful, and to be partially responsible, either directly or indirectly, for the production of hypertensive vascular disease. Kempner suggests, therefore, that the ordinary mixed diet may contain constituents that increase the production of these abnormal substances. By reduction of the elements of the diet that must be metabolized by the kidneys, the production of the abnormal substances is presumably reduced. This reasoning, *a priori*, accepts the renal etiology of hypertension. It is known that Kempner⁷ first used

*From the Hypertension Clinic, Massachusetts General Hospital.

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†Assistant in medicine, Massachusetts General Hospital.

‡Graduate dietitian, Massachusetts General Hospital.

§Associate physician, Massachusetts General Hospital.

the rice diet in treating hypertension resulting from kidney disease. Later, he extended the use of the diet to the treatment of essential hypertension.^{12, 14}

The enthusiastic reports of the treatment of essential hypertension with the rice diet by Kempner have stimulated many workers to attempt to evaluate this therapy.¹⁶⁻¹⁸ During the last year, in the Hypertension Clinic of the Massachusetts General Hospital we have used the rice diet as a method of treatment. Our study had been in progress for about nine months at the time this material was collected so that the number of patients is not large nor is the time elapsed sufficient to form conclusive opinions regarding the influence of this treatment on the course of such a disease as hypertension. We present this primarily as a progress report. In using the rice diet on clinic patients we hoped to determine whether this method of treatment is a practical one for use with ambulatory patients observed once a week while living in their normal surroundings and eating with other members of the family who are on a regular diet, and what clinical results are obtained when the treatment is applied to such a group.

METHOD

The patients in this study were taken from our regular clinic patients. Many had been followed for a number of years and therefore had a long control period, others were relatively new to the clinic and had a shorter control period. The group included patients with essential hypertension with and without renal involvement, the majority falling into the latter category. All patients were submitted to our routine workup, which includes history, physical examination, routine blood work, urinalysis, electrocardiograms, x-ray study of the chest, examination of the fundi, renal-function tests and determination of blood sodium, chloride, cholesterol, total protein and nonprotein nitrogen.

The patients advised to try the rice diet were seen weekly while on the strict rice diet. Although this made a heavy clinic load it was deemed important to follow the patients closely to pick up any evidence of sodium depletion in patients with poor renal function. Weights were recorded on admission to the clinic. At first each patient received individual instruction from the dietitian on the following diet:

- I. *Rice* Each day 1 cupful of rice, measured before cooking, is used. This yields approximately 4 cupfuls of cooked rice. Brown, polished or white rice may be used. It should be boiled or steamed without salt, milk or fat. (No butter, margarine, drippings, lard, grease or salad oil is used.)
- II. *Fruits* Fresh, raw or cooked fruits are taken. Any fruit with the exception of avocados, dates and nuts may be eaten (no tomatoes). No more than 1 banana a day is taken. Canned fruit is allowed, if no preservative has been added (all labels should be inspected, especially the fine print, which may

mention artificial flavor or color, sodium benzoate, sulfur dioxide or corn syrup). Frozen fruits may also be used.

III. *Sugar* Sugar is taken as desired (white only). Glucose (dextrose) may be used — it is less sweet and better tolerated by many people. Honey is permitted, but no maple sugar, corn syrup or molasses. Fruit and sugar jams and jellies — if pure — are allowed.

IV. *Fruit juices* Any fresh or canned fruit juice may be used if it contains no artificial flavor, color or preservative. Tomato juice and vegetable juice are not allowed.

V. *Fluids* Fluids are limited to 3 or 4 cupfuls of fruit juices a day. After the first three or four days, no additional water should be taken.

Special Instructions The patient is instructed to eat only the foods outlined on the diet and not to drink any tonics, root beer, sodas, gingerale or other carbonated beverages, no beer, ale, wine, whiskey, coffee or tea is permitted.

Later, the patients were seen in a group by the dietitian, and their problems were discussed and new ideas in fixing rice or fruit reported. There was a food display each week aimed at interesting the patients and demonstrating new methods of preparing rice or fruit combinations, using fruits that were currently in season. This produced a group motivation that we considered important in achieving close adherence to an unpalatable diet.

Each patient was seen individually at every visit by one of the doctors, who evaluated the symptoms as well as any physical changes that had occurred. The blood pressure was taken three times at each visit: on entrance, during the interview and just before departure. Modifications in the diet were ordered by the doctors, depending on the response to treatment, or if it became apparent that the patient was growing restive under such a stringent diet, modifications were made regardless of response. An attempt was made to follow Kempner's general plan in modifying the diet by the addition of items in the following order: white potato, low-sodium, nonleguminous vegetables, tea or coffee without milk, white meat of chicken, white fish or lean meat.

Several workers^{12, 19} have pointed out the importance of careful determination of the blood chemical constituents of patients on very low-sodium diets, especially those of patients with impairment of renal function. Our plan has been to order determinations (including sodium, chloride, cholesterol, nonprotein nitrogen and total protein) before the rice diet was started, and at frequent intervals (two weeks) while the patients were on the strict rice diet. In our experience a careful clinical follow-up study serves as a good protection for the patient. In the group of patients followed, only 1 developed a low serum sodium level (127 milliequiv per liter) and clinically this was apparent before the laboratory report had been returned.

The frequent determination of twenty-four-hour urinary chloride excretion is important to determine how closely a patient is adhering to the diet. On an average diet the excretion of urinary chlorides

varies from 125 to 175 milliequiv per liter in twenty-four hours, on the strict rice diet the excretion falls to 10 milliequiv or below. By use of this determination we separated our patients into the following classes: strict adherents, moderate adherents and delinquents. All patients whose urinary chloride excretion fell to 10 milliequiv per liter or below on the diet were called strict adherents, whereas those with excretions between 10 and 50 milliequiv were called moderate adherents, and those with excretions above 50 milliequiv were called delinquents. The moderate adherents could be rightly thrown out of the study, for this group does not represent patients on the Kempner diet. They do demon-

were men and 6 were women, whereas of the moderate adherents 5 were men and 15 were women. This division apparently points up one of the difficulties met with in treating patients in their normal environment: the women have to prepare the food for the rest of the family and are therefore subjected to greater temptation to deviate from the diet.

In evaluating the clinical results of this study, at present we shall limit ourselves to objective results as manifested by change in blood pressure and change in weight. Evaluation of renal, cardiac and cerebral status will be left until a later report.

What constitutes a significant reduction in blood pressure? This has been a difficult question to

TABLE 1 *Criteria for Evaluation of Blood-Pressure Response*

AUTHOR	TREATMENT	TYPE OF CASE	NO OF CASES	PERIOD OF OBSERVATION	METHOD OF EVALUATING RESPONSE
Berger and Fineberg ⁴	Effect of different amounts of sodium chloride on hypertension	Inpatient	11	Control 10 to 14 days treatment, 39 days.	Trend of blood-pressure curve
Bryant and Blecha ⁵	Low sodium diet forced fluids	Outpatient	100	Control period not stated treatment, weeks to 1 yr	Blood pressure fall to 135/95 diastolic fall to 95 or below
Fishberg ²³	Sympathectomy	Outpatient	119	Control months to years treatment, 4 to 6 yr	Diastolic pressure 25 per cent below preoperative level systolic 25 per cent below preoperative level blood pressure fall to 130/100 or less.
Flipse and Flipse ¹¹	Rice diet	Outpatient	54	Control period not stated treatment, 3 to 30 wk.	Decrease in mean arterial pressure of 20 fall of diastolic pressure to normal, increase in blood pressure more than 20/10 on modification of diet (uncontrolled)
Grollman et al. ¹⁰	Low sodium diet	Inpatient	6	Control, 2 wk treatment 57 to 129 days	Evaluation of blood pressure chart improvement equals drop to normal
Kempner ¹²	Rice diet	Inpatient and outpatient	500	Control 2 wk. treatment 2 to 6 mo	Improvement equals decrease of 20 in mean arterial pressure
Fanson et al. ²²	Potassium sulfocyanate	Outpatient	100	Control 1 to 3 mo treatment, months to 4 yr	Improvement equals fall of blood pressure to 150/100 sustained drop of systolic pressure of 30-50 sustained drop of diastolic pressure of 20-30
Contratto and Rogers ¹³	Rice diet	Outpatient	55	Control 3 yr treatment 6 mo	Decrease in blood pressure to 150/100 systolic drop of 50 diastolic drop of 20
Smithwick ²⁴	Sympathectomy	Outpatient	439	Control period not stated treatment 1 to 3 yr	7 categories (1-2-3—improvement, 4-5—unchanged 6-7—failure) 1—decrease in diastolic pressure of 20 or below 90 2—decrease in diastolic pressure of 20 but not below 90 3—decrease in diastolic pressure of less than 20 to no change pulse pressure narrowed ceiling levels lowered 4—diastolic and pulse pressure unchanged, ceiling lowered 5—no change in blood pressure 6—blood pressure higher 7—deaths

strate, however, a group of patients on a restrictive diet—one that is moderately low in sodium. It seemed of interest, therefore, to follow them so as to compare the results in this group with those obtained in patients on the strict rice diet.

RESULTS

The total number of patients instructed on the rice diet in nine months was fifty-six. Our success in maintaining patients on the diet can be shown by the following figures: strict adherents, 16 (28 per cent), moderate adherents, 20 (36 per cent), and delinquents, 20 (36 per cent). Of the group who adhered strictly to the rice and fruit diet, 10

answer, and has led us to a review of the literature, where one finds many criteria for evaluating change in blood-pressure levels.^{6, 8, 10, 12, 15, 18, 20, 22} Table 1 presents a summary of the criteria for evaluating blood-pressure response by different authors. As will be seen some studies are done on hospitalized patients, whereas others are done on ambulatory patients, the number of patients varies from 6 to 500, and the length of time from twenty days to five years. In some studies the blood-pressure response is based on a few records taken at long intervals, in others it is based on many determinations taken frequently over a short time. The control period, when stated, varies from weeks to three

years. It seems important for various workers to decide on criteria to be used in the evaluation of blood-pressure response so that communication of results in treatment will be facilitated.

The method we have used in evaluating blood-pressure response is to list all pretreatment clinic

control periods, the number of weeks on the diet and weight change.

In a sense the success or failure of any method of treating hypertension can only be assessed adequately after the last patient in the group dies. Only at that time does the complete influence of

TABLE 2 *Results of Rice Diet among Strict Adherers*

PATIENT	CONTROL PERIOD	INTERVAL ON DIET	BLOOD PRESSURE				ARTERIAL TENSION*			
			MEDIAN PRE DIET	MEDIAN POST DIET	CHANGE		PRE DIET	POST DIET	CHANGE	CHANGE IN WEIGHT
		wk			systolic	diastolic				kg
G. A.	10 yr	21	212/135	170/118	42	17	171	144	27	-3.8
E. B.	8 yr	4	180/105	155/100	25	5	142	126	16	-3.1
S. B.	7 yr	10	190/120	150/118	40	2	155	147	8	-3.5
W. DeS.	8 mo	23	170/110	140/100	30	10	156	119	37	-8.0
E. J.	12 mo	21	212/135	190/120	22	15	177	154	23	-4.1
J. K.	3 mo	22	170/100	140/100	30	0	139	119	20	-9.6
W. K.	7 mo	13	204/120	180/120	24	0	162	150	12	+1.8
N. Mc.	8 yr	23	205/130	170/108	35	22	168	135	33	-3.6
C. N.	5 mo	17	220/150	186/100	34	50	181	145	36	-3.4
D. P.	6 wk	10	215/110	190/100	25	10	165	147	18	-7.1
A. S.	3 mo	21	215/110	190/106	25	4	165	148	17	-1.7
T. S.	3 yr	10	230/130	170/104	60	26	168	159	9	-6.9
D. S.	6 yr	34	199/115	169/95	30	18	157	130	27	-3.5
V. V.	7 yr	5	190/132	130/96	60	26	192	147	45	-6.5
J. W.	20 mo	15	240/150	180/120	60	30	192	147	45	-2.5
P. Z.	25 mo	18	250/150	200/110	50	20	179	156	23	-4.9

*Kempner method (systolic plus diastolic pressure divided by 2 = mean)

blood pressures of a particular patient in numerical order, choosing the median and repeating this on the records taken during and after treatment. This method was used in an effort to eradicate the usual fluctuations due to emotional disturbances and other factors that one sees when blood-pressure determinations are made over a long period. If there

treatment on the natural course of hypertension become evident. It is to be hoped that we can report on the same group of patients again at a later date when the influence or lack of it becomes more apparent. At present, to indicate an improvement we have chosen a reduction of 20 in the median diastolic pressure. On this basis 6 out of 16 pa-

TABLE 3 *Results of Rice Diet among Moderate Adherers*

PATIENT	CONTROL PERIOD	INTERVAL ON DIET	BLOOD PRESSURE				ARTERIAL TENSION*			
			MEDIAN PRE DIET	MEDIAN POST DIET	CHANGE		PRE DIET	POST DIET	CHANGE	CHANGE IN WEIGHT
		wk			systolic	diastolic				kg
A. A.	16 mo	9	210/100	190/90	20	10	155	139	16	-4.7
C. B.	13 mo	10	190/118	170/106	20	12	155	142	13	-2.3
P. B.	3 yr	32	220/120	177/106	43	14	167	142	25	-2.7
O. C.	7 mo	15	202/128	200/120	2	8	168	160	8	+2.1
N. C.	7 mo	19	200/108	180/96	20	12	151	135	16	None
H. E.	2 mo	17	250/130	200/108	50	22	187	155	32	-0.7
J. F.	3 mo	3	221/122	220/123	-1	+1	171	171	0	+4.9
G. H.	4 yr	3	192/120	193/110	+1	-10	158	148	10	-4.6
O. J.	49 mo	27	200/120	180/110	20	10	169	141	28	-2.0
M. Mc.	6 yr	4	175/130	141/110	34	20	156	126	30	-7.7
K. Mc.	5 mo	22	182/117	170/110	12	7	156	158	18	+4.4
M. Mc.	28 mo	8	234/126	180/120	54	6	179	158	21	-3.1
T. Mc.	5 yr	19	216/132	180/130	36	2	174	155	19	-3.6
V. V.	18 mo	3	210/120	200/110	10	+10	166	164	2	-0.7
L. V.	26 mo	11	200/120	180/110	20	10	152	129	23	-3.0
M. R.	6 yr	5	232/126	142/94	19	17	135	125	10	-2.1
T. S.	18 mo	12	161/111	137/92	24	18	135	117	18	+1.5
P. S.	9 mo	7	190/110	137/92	53	18	155	117	38	-1.9
D. W.	2 mo	34	215/140	223/150	8	10	177	179	2	-4.3
C. W.	6 yr	9	185/105	160/95	25	10	151	127	24	-

*Kempner method (systolic plus diastolic pressure divided by 2 = mean)

has been a sustained change, it is evident, but the peaks and hollows are ironed out. In tabulating our results (Table 2 and 3) we have used the method described. For comparison we have applied Kempner's¹² method of evaluating blood-pressure change to our cases. We have included in the table the

tients, or 37 per cent of those who stayed strictly on the rice diet, showed an improvement in blood pressure. When Kempner's method was applied to this group, 10 out of 16 patients, or 62 per cent, revealed an improvement in blood pressure. In the group of patients whom we termed moderate

adherers, 3 out of 20, or 15 per cent, demonstrated improvement, whereas by Kempner's criterion 9 of 20, or 45 per cent, would be considered improved. On the other hand, if a drop of blood pressure to 150 systolic, 100 diastolic, was used as a sign of improvement, as several workers have done,^{18 20 21} 4 of 16, or 25 per cent, in the strict group showed improvement whereas 4 of 20, or 20 per cent, in the moderate group showed improvement. As can be seen from this comparison the number of patients who show improvement in blood pressure on any one type of treatment is dependent on the criteria used for evaluating the improvement. When all is said and done we have no way of knowing at present whether reduction in blood pressure constitutes an improvement in the hypertensive state.

Correlation of weight reduction to change in blood pressure has long interested clinicians. No valid conclusion can be drawn from such a small group. If, however, we consider a loss of 4.5 kg, or 10 lb, as a significant weight change, 7 out of 16 strict adherers showed a significant change. Of this number 4 demonstrated a diastolic drop of 20 or more. Of 20 moderate adherers, 5 showed a significant weight change, and only 1 of the 5 showed an improvement in blood pressure.

The other criteria ordinarily used in the evaluation of improvement in the hypertensive state, such as change in electrocardiogram, heart size on x-ray study, fundal vessels and renal-function tests, have not been analyzed for this report. A rapid survey indicates that little change has taken place in the various areas as manifested by these tests.

CONCLUSIONS

The rice diet has been used in the treatment of a group of outpatients living at home in their normal environment. The method can be used with safety so long as the patients are carefully followed at frequent intervals.

A significant drop in blood pressure occurred in 6 of 16 patients, or 37 per cent, who adhered strictly to the diet, and in the group of moderate adherers a significant drop occurred in 3 of 20 patients, or 15 per cent.

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ASPIRATION OF THE ELBOW JOINT IN THE TREATMENT OF FRACTURES OF THE HEAD OF THE RADIUS*

T. B. QUIGLEY, M.D.†

BOSTON

IN RECENT years there has been a revival of the principle of early active motion in the treatment of elbow fractures, first expounded by Jean Pierre David¹ in 1779 and vigorously restated a century later by Lucas-Championnière.² For fractures of the radial head in particular this concept appears to be well accepted. In general, these fractures fall into three groups: those in which the fragments are so comminuted or displaced as to require arthrotomy, those in which the fragments are displaced, motion is limited, and arthrotomy is contemplated, and those in which impaction and displacement are minimal.

For the first group, prompt excision of the radial head followed by early active motion is indicated.

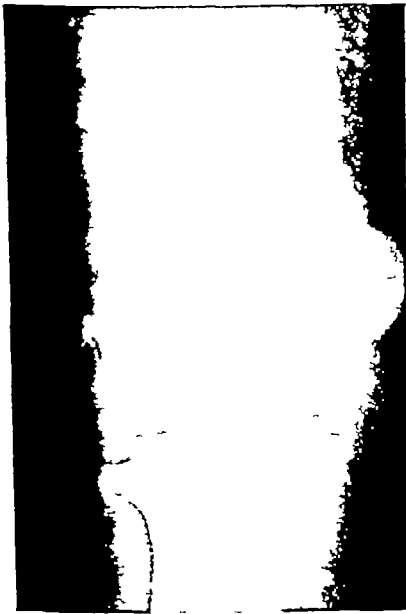


FIGURE 1 Depressed, Displaced, Wedge-Shaped Fracture of the Radial Head (Case I)

There was normal elbow motion after aspiration of 11 cc of thick, bloody fluid.

For the second and third groups, minimal immobilization results in rapid restoration of function and a low incidence of subsequent myositis ossificans traumatica.³

Active motion, however, although easy to prescribe, is often difficult for the patient to achieve. Relief of pain and marked increase in range of motion very often follow aspiration of the joint. The

literature contains several pleas for early active motion,³⁻⁵ but little note has been taken of aspiration in treatment other than the descriptions of Postlethwait,⁶ Jacobs and Kernodle¹⁰ and Buffing-

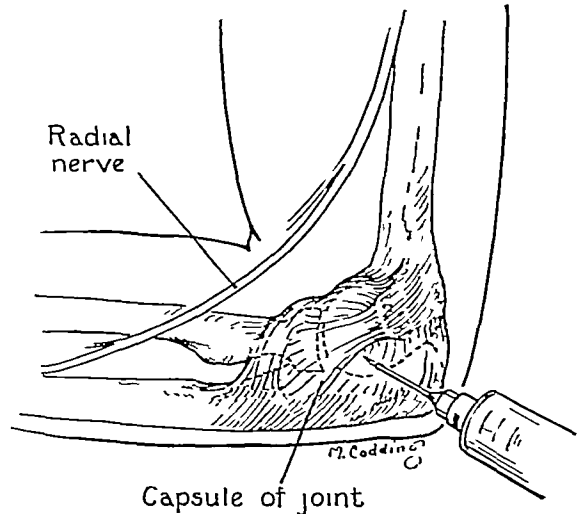


FIGURE 2 Technic of Aspiration

With the forearm pronated, after infiltration with procaine, a 16-gauge needle is introduced into the center of the triangle formed by the head of the radius, the lateral epicondyle of the humerus and the tip of the olecranon.

ton¹¹ of its use in fractures of the radial head in soldiers.

The following case is typical of the second group of fractures—those with limitation of motion and moderate displacement of the fragments.

C. W., a 42-year-old housewife, was first seen 48 hours after a fall down a flight of stone steps on her outstretched left arm. Active and passive flexion and extension at the elbow were limited to the middle third of the normal range, as was rotation of the forearm. X-ray examination disclosed a depressed, displaced wedge-shaped fracture of the anterolateral aspect of the head of the radius (Fig. 1).

Arthrotomy was contemplated because of the size and shape of the fragment, which, it was believed, was acting as a mechanical block to rotation. However, after aspiration of 11 cc of thick, bloody fluid, active and passive flexion, extension and rotation were normal. Active exercises were started, and 2 months later function of the two elbows was indistinguishable.

Aspiration is not carried out for at least 24 hours after the injury, lest the hemarthrosis recur. The technic is simple (Fig. 2). However, no aspiration of a joint should be undertaken casually as an office procedure. The resistance of joints to infection is low, and no antibiotic can take the place of a clean operating room, meticulous skin disinfection and rubber gloves.

*From the Surgical Service, Peter Bent Brigham Hospital and the Department of Surgery, Harvard Medical School.

†Associate in surgery, Harvard Medical School; associate in surgery, Peter Bent Brigham Hospital; surgeon, Harvard Athletic Association.

With the forearm pronated to minimize the possibility of injury to the deep branch of the radial nerve,¹² and after infiltration with procaine, a 16-gauge needle is introduced into the joint through the center of the triangle formed by the head of the radius, the tip of the olecranon and the lateral

Rapid return of function after aspiration in the third group of fractures, those with minimal impaction or displacement, is illustrated by the following case

G K., a 40-year-old brakeman, tripped over a rail, striking his right elbow. When he was first seen, 4 days later,

TABLE 1 Results of Aspiration in Treatment of 7 Cases of Fracture of the Head of the Radius

PATIENT	SEX	AGE	TYPE OF FRACTURE	MOTION BEFORE ASPIRATION	AMOUNT OF FLUID ASPIRATED	RESULT
J J S	M	49	Comminuted impacted but not deformed	Patient "unable to move without pain"	15	Immediate full range of motion function normal 4 days later
W D	M	16	No displacement	Rotation normal, flexion and extension limited to 15°	5	Patient immediately able to extend and flex to 45° rotation normal function normal 2 mo later
J K	F	46	No displacement	Flexion and extension very limited" normal rotation	10	Immediate improvement function normal 2 mo later
V A	F	37	Downward depression and slight impaction of lateral aspect	"Elbow moves only between 90° and 140°" rotation, 10°	10	Immediate return to 50°-175° function normal 6 wk. later except for 10° loss of pronation
A. M. C.	F	61	No displacement	"Motion greatly limited"	15	Immediate return to 150°-80° with normal rotation normal function 3 mo. later
G K.	M	40	No displacement	"Marked limitation of motion and pain"	14	Immediate normal range of motion function normal 2 wk. later
M. W.	F	42	Wedge-shaped displacement	Flexion, extension and rotation limited to middle third of normal range	11	Immediate free range of painless motion, function normal 2 mo later

epicondyle of the humerus. Often, bloody fluid under considerable pressure is encountered. This is to be expected since the normal fluid content of the adult elbow joint is less than 1 cc,¹³ and more than 10 cc is frequently recovered. Aspiration in this group of fractures does not take the place of

flexion and extension of the elbow were limited to 30°, and rotation of the forearm to 15°. X-ray examination disclosed a fracture of the radial head with minimal displacement (Fig 3). After aspiration of 14 cc of thick, bloody fluid, the range of active motion of the elbow was normal and painless. The patient returned to work 12 days after the injury and 8 days after aspiration.

The results in 7 consecutive cases treated at the Peter Bent Brigham Hospital are summarized in Table 1.

SUMMARY

Attention is called to the usefulness of aspiration of the elbow joint in the treatment of undisplaced fractures of the radial head, and also in clarifying the indications for arthrotomy in fractures with moderate displacement.

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FIGURE 3 Fracture of the Radial Head with Minimal Displacement (Case 2)

There was normal elbow motion after aspiration of 14 cc of thick, bloody fluid.

arthrotomy and excision of the radial head when indicated. The persistence after aspiration of limitation of motion or palpable grating on passive rotation is an indication for operation. Arthrotomy should not be delayed, and the decision can almost invariably be made at the time of aspiration.

BOSTON MEDICAL LIBRARY

Report of the Librarian*

IT IS again the duty of the Librarian, as provided by the by-laws, to present to the Corporation of the Boston Medical Library his annual report — his eleventh accounting of the state of the Library since he took office in 1938. In growth, service to its readers, quality of accessions and increase in personnel, the Library had in 1948 the most profitable year in the seventy-three years since it was organized in 1875. More books and journals were used by readers in the past year than ever before: 10,000 more than in 1947, the year of largest use up to 1948. As the attendance in Holmes Hall did not exceed the average of the last decade, this use came largely through the growth of inter-library loans to non-members and, more particularly, by way of professional members — libraries in hospitals and medical schools who borrow for our own fellows and for nonfellows as well.

The total membership of the Library remained practically unchanged at a little over 1100. The increased use of the Library presumably came from the 5671 Massachusetts Medical Society members who, using our books in hospital libraries and elsewhere, solved their medicoliterary problems. It makes little difference where our books and journals are used — in hospital, laboratory or home — as long as they fill the needs of some doctor for the printed record of his contemporaries or those who have gone before. The Library has one primary aim — service to all. In supplying the needs of a growing body of physicians and scientists, the Library grows also — in size, in quality, in resources and in availability. Use is the best barometer of worthiness, on that score we can report a rising glass.

On December 31, 1948, the books and volumes of periodicals in the Library were 206,564 and, in addition, 147,144 pamphlets were catalogued and available for use. The circulation during the year was 53,518 items, the attendance 10,089. The inter-library loans to nonmembers had grown to 1798 — all figures far in excess of those for 1947 and showing a healthy increase in all departments.

THE USABLE PAST

Only by a knowledge of the usable past can one evaluate the foreseeable future. To the Librarian the past is all printed material, even the latest number of a current periodical. The immediate past is naturally the primary test, since the Library aims to provide for its fellows, the Massachusetts Medical Society members and the public all the printed records of contemporary research that are likely to be called for by clinicians and students. Secondly, we try to make available in a reasonable time other

material that we do not possess, taking advantage of our neighborhood libraries, the great repositories of Harvard University and the Massachusetts Institute of Technology, as well as many others that go, with ours, to make up the cultural heritage of Greater Boston.

In the older literature of medicine, I need not remind you, we are rich indeed. To the great works of the past we constantly add — in 1948 we acquired three unique manuscripts and eighteen books of medical interest printed before 1501. Among the incunabula are some of considerable interest, reflecting fifteenth-century medicine as it was recorded in the early days of printing with movable type. Another edition of the works of Michele Savonarola was added to the two acquired in 1947. We now lack only two of this author's publications in our incunabula holdings, having ten of the dozen issued before 1501.

ACCESSIONS

Incunabula

Two early tracts on syphilis were acquired in 1948. Johannes Widmann's *De pustulis, sive mal de françois* (Strassburg, 1497), and Gaspar Torrella's *Dialogus de dolore cum tractatu de ulceribus in pudenda* (Rome, 1500). The Library has some of the most important of the syphilis literature of the fifteenth century, including Schellig (1495), two tracts by Grünpeck (1496, 1497) and Leonicensio (1497). We lack the first editions of both of the Grünpeck books, and the tracts by Torrella, Gilino, Stäber, Montesauero and Scanaroli. Some are only known in a few copies and may never come into the market. Of the ten that were produced in facsimile by Sudhoff and Singer in 1925, the Library has three. The list, with the Klebs numbers, is shown in Table 1.

Hans Widmann, born in 1440, studied medicine in Italy but took his degree in Freiburg in 1474. After 1484 he was professor of medicine at Tübingen, where he also served as inspector of "lepers." His tract on syphilis was completed on January 20, 1497, when he sent it to Johann Nell, a physician and friend at Strassburg, where it was printed, probably in the spring of that year. Sudhoff and Singer knew of only four copies, since 1925 two more, including ours, have been recorded. The book was reprinted a few months later in Rome. Widmann called syphilis, as Schellig did, the French disease, both following the Edict of the Diet of Worms (1495), which they attended. Widmann made a differential diagnosis between leprosy and

*Read in part at the annual meeting of the Boston Medical Library March 1, 1949.

†Sudhoff K. Adapted by Singer C. *The Earliest Printed Literature on Syphilis Being Ten Tractates from the Years 1495-1498*. 352 pp. Florence, 1925.

syphilis, for he was long familiar with the former disease. He advised standing on the windward side of the syphilitic, a common practice in his time in dealing with lepers. In treatment, Widmann used mercury as had his predecessors. The Library also owns Widmann's *De pestilentia* (Tubingen, 1501) containing the reference to *malum franciae* in 1457, a date that seems quite improbable and may be a printer's error for 1495 or 1497. As Sudhoff says, "It is a matter on which we can only conjecture."

Of more importance was the work of Gaspar Torrella, who left his native city of Valencia in

Unfortunately, only three copies seem to have survived, none have reached America. A later work of Torrella, printed in Rome in 1500, attacks the subject in a lighter vein — a kind of prelude to the style of Fracastor's poem on syphilis of 1530. It is this book that was acquired by the Library in 1948.

Sixteenth-Century Imprints

Torrella's publication in 1500 brings us into the sixteenth century, an age of increasing output of medical works, for the presses were hard pushed to keep up with a growing demand for the easily transported book, movable in pocket or saddlebag, that could be used in the same text and at the same time by doctors in Cracow, Montpellier and Edinburgh. Thus, there took place a vast spreading of knowledge, not dreamed of before the days of printing. Having catalogued our fifteenth-century books in 1944 and recorded our addenda of incunabula in the *Report of the Librarian*, year by year, the Library is in the process of segregating its sixteenth-century holdings for convenience of recataloguing and adds to this new class of books as fast as funds will permit. Over sixty books printed before 1600 were acquired in 1948, including the pest ordinances of Antwerp for the years 1575, 1578, 1580 and 1586, an anti-pest tract by Cermisonus (Milan, 1512), Gesner's *Schatz* (Zurich, 1555), and the famous *Malleus maleficarum* by Sprenger and Institoris, in editions issued at Cologne (1520), Lyon (1584) and Frankfurt (1588).

Americana

In the field of Americana a few texts were added. Perhaps the most important were copies of the *Christian Watchman*, a Boston newspaper, for October 23, 30 and November 6, 1846, containing what appears to be an eye-witness account of the second ether operation at the Massachusetts General Hospital on October 17, 1846, and possibly of the first operation the day before. Medical letters include one by O. W. Holmes relating to his son's injury during the Civil War, correspondence from Zadok Howe to Moody Kent (1812-1827) and twenty-three letters from James Thacher, many to his daughter, written from Plymouth, 1784-1824.

Special Gifts

As usual the Library added many gifts from our fellows and friends. The list is a long one and the Library, as in the past, reflects the devotion of its users, whether fellows, members, hospitals or medical schools. The Harvard Medical School Library continued to send us inaugural dissertations and theses, as well as current Russian literature — classes of material that we, by mutual agreement, have arranged to keep in the Boston area. Dr. George Kelemen supplied us with Hungarian periodicals, Dr. Stephen Rushmore gave us a large part of his personal library and allowed us to purchase from

TABLE 1 The Earliest Printed Literature on Syphilis for the Years 1495-1498

AUTHOR	TITLE	KLEBS No.
Schellig*	<i>In malum de Francia consilium</i> [Heidelberg 1495]	891 1
Grünpeck	<i>De pestilentia scorra</i> [Augsburg 1496]	476 1
—*	[Nürnberg 1496-7]	476 2
—	<i>Ursprung des bösen Franzos</i> Augsburg 1496	477 1
—*	[Nürnberg 1497]	477 2
Leonicensi*	<i>De morbo gallico</i> Venice 1497	599 1
Torrella	<i>Morbum gallicum</i> Rome 1497	979 1
Widmann*	<i>De pustulis sive mal de franço</i> [Straßburg 1497]	1048 1
Gilino	<i>De morbo gallico</i> [Ferrara 1497]	463 1
Staber	<i>A morbo Gallorum</i> Wien [1497-8]	931 1
Montesano	<i>Mal franzoso</i> [Bologna 1498]	691 1
Scanaroli	<i>De morbo gallico</i> Bologna 1498	887 1

*In Boston Medical Library

Spain in the late fifteenth century to seek his fortune in Italy. Coming from a well known medical family, this energetic young doctor was welcomed in Rome by a fellow-countryman, Roderigo de Borgia. The wily Roderigo, already a wealthy cardinal, bought up enough votes in 1492 to become Pope Alexander VI, and Torrella became his body physician and the medical adviser to the papal household. Among the Borgia family and the papal court, Gaspar had, in spite of his restricted chentele, a considerable experience with syphilis. During September and October, 1497, for instance, the papal physician treated seventeen cases of the *morbo gallico*. One of his patients was Cesare Borgia, the profligate son of the Pope, who, at the age of sixteen in 1493, had been made a cardinal by his father.

In Torrella's first publication, a tract of twenty-four leaves, issued in Rome in 1497, 5 typical cases are described. All were treated by mercurial ointment. The case presentations are "first hand," and this little pamphlet is the most valuable of all the early literature on syphilis. One of the case histories is almost certainly that of Cesare Borgia

him a few of the more expensive items, much to our advantage, books and periodicals were received from the estates of Abraham Myerson, Richard F. O'Neill, Isadore E. Reid and George H. Torney, a substantial bequest was received from the estate of Walter P. Bowers, the Suffolk District Medical Society continued its support, and miscellaneous gifts were received from many others.

LIBRARY ACTIVITIES

Addresses and Meetings

The Librarian addressed the annual meeting of the Cleveland Medical Library Association on January 16, 1948, reading a paper, "A Roving Commission. The doctor calls on some of his friends," describing a sojourn with Sir William Osler in Oxford in 1916 and a visit to the home of Arnold C. Klebs at Nyon in Switzerland in 1939. On February 10 he gave the Walter Reed Lecture before the Section on the History of Medicine, Richmond Academy of Medicine, entitled "James Thacher and His Influence on American Medicine," and was made an honorary member of the Section. The Librarian also visited, during the course of the year, the Army Medical Library, the medical libraries of the University of Minnesota, the Rhode Island Medical Society, the College of Physicians of Philadelphia, the John Crerar Library, Chicago, the St. Louis Medical Society and the Welch Medical Library, Baltimore. The Librarian attended the Section on the History of Medicine at the annual meeting of the American Medical Association, held in June in Chicago, and the meeting of the Honorary Consultants to the Army Medical Library in Washington, October 21 and 22, as chairman of the Committee on the History of Medicine. He was elected president of the American Association of the History of Medicine for two years at the annual meeting in Philadelphia in May.

The Director also attended the meeting of the Honorary Consultants to the Army Medical Library in Washington in October, the meeting of the Medical Library Association in Philadelphia in May and that of the Special Libraries Association in Washington in June.

In February the Library entertained in Boston Dr. Josep Trueta, formerly of Barcelona and now of Oxford, the authority on Servetus and author of *The Spirit of Catalonia* (London, 1946), and, in April, Dr. Douglas Robb, of Auckland, New Zealand. Both visited the Library, much to our profit.

Book Reviews

About 270 new books, received from the *New England Journal of Medicine*, were reviewed by the fellows and staff of the Library in 1948, either by short notes or by longer, critical reviews (about 80). Nearly 100 reviewers perform this task as a contribution to the Library. This service, one of outstand-

ing merit, brings to the Library promptly many of the latest publications in medical literature and the new editions of older books for the benefit of our readers.

Exhibits

At various times during this year small exhibits were arranged in the Osler Exhibit Cases (donated to us by Osler from his Ingersoll Lecture honorarium of 1904) in the rotunda of the Library, largely of the chief current accession, complemented by other works in the Library. Among the books shown in 1948 were the writings of Giovanni Michele Savonarola (1384-1462), the Paduan physician. Also on exhibit were a collection of medals and tokens, illustrating medical numismatics, including the Baker Clinic diabetic medals recently presented to the Library by Dr. Joslin, and a portrait and the original article on DDT in honor of Paul Mueller, winner of the Nobel Prize in Medicine for 1948.

Conferences

A conference with nineteen of the medical librarians of Metropolitan Boston was held at the Library on October 30, 1948. The Director acted as chairman for the discussion of various library problems including library statistics, losses and their control, co-operation and the relation of the Boston Medical Library to other medical libraries, damaged material, foreign periodicals and their coverage, inter-library loans and other topics. Consideration was given to the possibility of organizing the conferences on a semi-official basis, and it was agreed that this should be done, with at least two meetings a year and at different libraries.

Publications

Recent articles emanating from the Library are as follows:

Seventy-second Annual Report of the Boston Medical Library for the Year 1947. Boston privately printed, 1948.

Phippen, W. G. Boston Medical Library. Report of the president. *New Eng J Med* 239:83-84, 1948.

Viets, H. R. Boston Medical Library. Report of the librarian. *New Eng J Med* 239:84-89, 1948.

Idem. History of neurology in last one hundred years. *Bull New York Acad Med* 24:772-783, 1948.

Idem. Roving commission doctor calls on some of his friends. *Bull Hist Med* 22:362-372, 1948.

Editorial. Wotton and Trueta on Servet. *New Eng J Med* 238:887, 1948.

Editorial. Sherrington's classic contribution to neurophysiology. *New Eng J Med* 239:101, 1948.

- Ballard, J F History of the Medical Library Association *Bull M Library A* 36 227-241, 1948
 Idem Notes from Boston Medical Library *New Eng J Med* 239 490, 1948
 Editorial Manuscripts and medical history *New Eng J Med* 239 723-725, 1948

VARIA

A few of the books of unusual interest to medical scholars, published recently, deserve notice *Pioneer Life in Kentucky, 1785-1800*, by Daniel Drake (New York, 1948), edited from the original manuscript by Emmet Field Horne, was first issued in 1870. Dr Horne went back to Drake's original letters, now in the Cincinnati General Hospital and long out of print, as is a reprinting of 1907, only to find that previous editors had taken many liberties. The book, now edited with scholarly accuracy, is not a medical treatise, but a portrayal of farm and family life by the most eminent early nineteenth-century physician of the Central West. Another physician, George W. Corner, has performed a similar task for Benjamin Rush, editing his autobiography from the original manuscript for the American Philosophical Society *The Autobiography of Benjamin Rush His "Travels Through Life" together with his commonplace Book for 1789-1813* (Princeton, 1948) is superbly and meticulously documented by Corner, with numerous illustrations. A delight-

ful book of essays is *Wayfarers in Medicine* (London, 1947), by William Doolin, the editor of the *Journal of the Royal Academy of Medicine in Ireland*, a salty, varied series of sketches ranging from "Graeculi Esurientes" to "Osler." Among the best are "Some Old Journeyman Surgeons" and "Pathfinders in Dublin." Sharp, too, is *Rabelais* (London, 1948) by John Cowper Powys, a translation of his life story and an interpretation of his genius. Powys, in a thoughtful book, takes you "on sunny morning stops" where Rabelais meets his friends. One notes further *The Legacy of Swift A Bi-Centenary Record of St Patrick's Hospital, Dublin* (Dublin, 1948), *Dr Kirkbride and his Mental Hospital* (Philadelphia, 1947), by Earl D. Bond, *The Story of St Thomas's 1106-1947* (London, 1947), by Charles Graves, *Encyclopedia of Medical Sources* (Baltimore, 1948) by Emerson Crosby Kelly, *The Physicians of Essex County* (Salem, 1948), by Russell Leigh Jackson, *Religio Medici* (Lund, 1948), by Thomas Browne, translated into Swedish by Ernst Abramson, a provocative book, *Surgery Orthodox and Heterodox* (Oxford, 1948), by Sir William Heneage Ogilvie, and *Selected Writings of William Clowes* (London, 1948), with a delightful introduction by F. N. L. Poynter, of the Wellcome Historical Medical Museum.

HENRY R. VIETS

MEDICAL PROGRESS

NEUROPHYSIOLOGY, 1942-1948 (Concluded)*

JOHN F. FULTON, M.D.†

NEW HAVEN, CONNECTICUT

THE PYRAMIDAL SYSTEM AND THE MOTOR AREAS

The Pyramidal System

An even more profound modification has taken place in beliefs concerning the origin and nature of the pyramidal system. Current texts in neurology generally state that the pyramidal tracts take origin from the giant cells of Betz in the motor area (area 4) and from a few similarly large cells in the parietal cortex. This view is based largely upon the studies of Holmes and May,⁶¹ published in 1909, these authors having found in cases of spinal transection in man that retrograde degeneration in the cerebral cortex was limited to the cells of Betz. Lassek, in a series of 19 papers on the pyramidal tract of man and animals,[‡] finds that whereas there

is an average of 34,000 Betz cells in a given hemisphere (that is, cells between 900 and 4100 sq microns in size), there are 1,000,000 fibers in a human pyramid. This discrepancy between numbers of Betz cells and fibers in the pyramid indicates that the Betz cells can contribute at most 2 or 3 per cent of the fibers in the human pyramid, and that the greater proportion must come from some other source. The Betz cells no doubt give rise to the larger fibers in the pyramid, for fibers of large diameter increase in proportion as the primate scale is ascended, and so does the size of the Betz cells.

In attempting to discover from what other parts of the cerebral cortex the pyramidal tract might arise, Woolsey and Chang⁶² have carried out the ingenious experiment of leading off electrically from the surface of the cortex while the pyramids are being stimulated antidromically at the level of the medulla. Using rabbits, cats and monkeys they find that an antidromic action potential can

*From the Department of Physiology, Yale University School of Medicine.

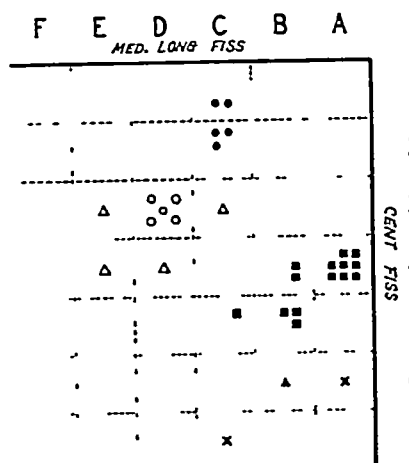
†Sterling Professor of Physiology, Yale University School of Medicine.

‡These papers are summarized in the 1948 volume of the Association for Research in Nervous and Mental Disease.⁶³

be detected over wide areas of the cortex in all three species, including fields 6, 4, 3-1-2, 5 and 7 of Brodmann. In the monkey and cat two waves can be detected—a fast one, which is most conspicuous in area 4 (and its counterpart in the cat), followed by a slow wave, which is present in all the areas just mentioned. In the cat the slow wave is much larger relatively than the fast wave, and in the rabbit only the slow wave can be detected. These findings are in harmony with the belief that the faster spike wave represents the contribution of the large fiber components, for in the rabbit there are no large fibers, and in the cat the proportion of large fibers is much smaller than that in the monkey (Lassek). It becomes necessary, therefore, to regard the pyramidal tract as taking origin from the entire precentral convolution as well as from the full extent of the parietal lobe, and it is therefore concluded that only the fast fiber components are primarily restricted to area 4.

The effects of *interruption* of the pyramidal tract at the level of the pyramid have also proved surprising in the light of earlier neurologic teaching, for the spasticity that was thought to be characteristic of an upper motor neuron lesion is completely lacking, indeed, Tower⁶⁴⁻⁶⁵ finds, both in monkey and chimpanzee, that the skeletal musculature on the affected side is flail and that the muscles themselves undergo conspicuous atrophy as a result of disuse. This result was scarcely surprising since it was known that similar flaccidity is seen after isolated lesions of area 4 in chimpanzees, such lesions, however, involve extrapyramidal, as well as pyramidal, projections. This no doubt accounts for the transient digital spasticity that Denny-Brown and Botterell^{65a} observed in monkeys after partial lesions of area 4. The flaccid character of the paresis seen by Tower makes imperative some modification of the older view, espoused by Walshe⁶⁷ and others, that all the phenomena following interruption of the corticospinal system are to be interpreted as "release phenomena." Thus, Tower writes "In the realm of motor function the condition is unquestionably one of deficient function without phenomena of release," adding that "there is no evidence of inhibitory function [in the pyramidal system]." Walshe⁶⁷ objects to this interpretation, for he contends that the Babinski plantar response must be looked upon as an example of release of a phasic nociceptive reflex from cortical control. The point is perhaps an academic one, but if Dr Walshe will accept flaccidity and atrophy as an essential part of the pure pyramidal syndrome in man and the higher primates, one will not begrudge his insistence that the Babinski reflex is to be regarded as a release phenomenon. Denny-Brown⁶⁶ characterizes Tower's classic description of the effect of pyramid section as "the final blow to the clinical conception of disorder of the pyramidal system," but Walshe considers such an obituary premature.

It may prove more difficult to bring Dr Walshe to terms on the question of whether individual muscles find representation in the motor area, or only movements. Believing that the controversy could be resolved more readily by recourse to experiment than by philosophic reflection, Chang, Ruch and Ward⁶⁸ isolated eight representative muscles in a series of monkeys, attaching each muscle to separate myographs, they then explored the responsiveness of several muscles to unipolar stimulation of various foci on the motor area. With minimal intensity of stimulation they found that certain points gave "solitary responses,"—that is, an isolated reaction of a single muscle unaccompanied by contraction of any other muscles under observation. Such a group of solitary reactions is shown in Figure 6. Not only were individual muscles rep-



- M. Extensor Digitorum Longus (EDL)
- M. Extensor Hallucis Longus (EHL)
- ▲ M. Tibialis Anticus (TA)
- × M. Abductor Hallucis Longus (AHL)
- M. Flexor Digitorum Longus (FDL)
- △ M. Tibialis Posticus (TP)

FIGURE 6 Distribution of Cortical Foci for Different Muscles from Which Solitary Responses Can Be Obtained (Reproduced from Chang, Ruch and Ward⁶⁸ with the Permission of the Publishers)

resented, but in some instances small portions of a given muscle were separately stimulable.

In discussing their results, Chang and his associates write

Inspired by the dictum of Hughlings Jackson that movements rather than muscles are represented in the motor cortex other investigators have emphasized the instability of the cortical mosaic and a multiplicity and diffuseness of representation of muscles in the motor cortex. This formulation leaves out of account the fact that a somatic movement, however complex, is produced

by the contraction of muscles. As a consequence, at some level, muscles must be represented as muscles so that they can be manipulated and organized into movements.

Hines⁶⁹ is even more outspoken:

The above study indicates that in the precentral gyrus of the macaque there is a detailed pattern of representation of the skeletal muscular system and that the basic plan of this pattern can be analyzed in terms of muscles. Thus, although there is overlapping of cortical fields for peripheral cutaneous areas, individual muscles are represented maximally in specific parts of the precentral gyrus, just as areas of skin are represented maximally at particular points on the postcentral gyrus. This does not mean that a particular muscle is the only muscle represented at a specific cortical point, but that it is the one predominantly represented there.

The maps of muscle foci observed by Chang et al suggest that "the Betz cells for a particular muscle

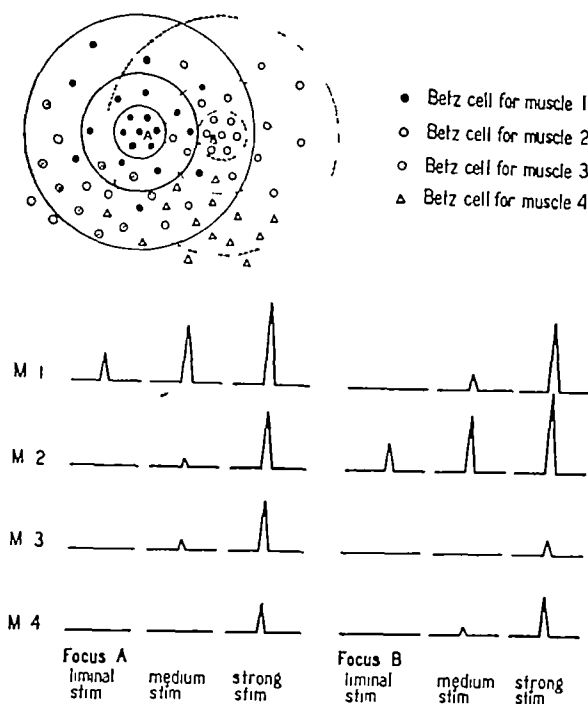


FIGURE 7 Diagrammatic Representation of the Hypothetical Distribution of Betz Cells for Individual Muscles with Cell Group for Each Muscle Having a Focal Distribution and an Overlapping Fringe

Each symbol stands for a Betz cell, and the large concentric circles represent the sphere of excitation. The expected contraction of the muscles in response to cortical stimulation at different strengths is shown by the curves drawn in the lower part of the figure, in which the magnitude of the contraction is determined by the number of Betz cells involved in the sphere of excitation. (Reproduced from Chang, Ruch and Ward⁶⁸ with the permission of the publishers.)

are distributed over a contiguous area of the cortex with the highest cell concentration located at a particular focus within that area, and that the farther from that focus, the more sparsely scattered are the Betz cells devoted to that muscle." They thus envisage a considerable overlapping of the

fringes of each field of Betz cells, which is illustrated schematically in Figure 7.

Broadly considered, the pyramidal tract must be regarded, as Sherrington originally insisted in *The Integrative Action of the Nervous System*, as an internuncial pathway between the motor mechanism of skeletal muscle and the distance receptor impinging upon the higher levels of nervous function. As Walshe⁶⁷ has aptly put it, the pyramidal tract "is a sort of common path standing between the receptors and the motor mechanisms of the nervous system." This view should have the hearty concurrence of those who have performed experiments in this field.

The Motor Area

Perhaps the most notable advance in the sphere of the motor area has been Rasmussen and Penfield's⁷⁰ résumé of their experience in stimulating the precentral and postcentral convolutions during 206 operations (principally under local anesthesia).

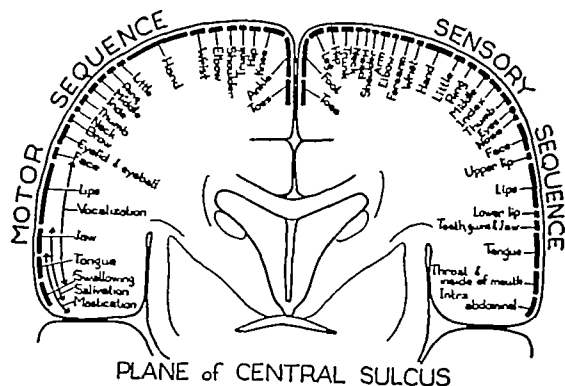


FIGURE 8 Motor and Sensory Sequence in the Human Cerebral Cortex

This is based on observations in 222 operations carried out under local anesthesia. (Reproduced from Rasmussen and Penfield⁷⁰ with the permission of the publishers.)

on 186 patients and their more recent report on stimulation of the human eye fields.⁷¹ The sequence of sensory representation in the postcentral gyri had long been thought to correspond with that of the precentral motor cortex, but these observers find that the sensory projections of the head fall between trunk and arm (Fig 8). Their illuminating summary may be quoted:

1 As a result of further stimulation studies in man, certain modifications in the sensory sequence are suggested: (a) The head as a whole is represented between trunk and arm. (b) Neck sensation seems to belong between the head representation and trunk. (c) Tongue sensation has been moved to below teeth, gums and jaw, conforming to its location in the motor sequence. (d) Taste has been eliminated from the sequence of the cortical convexity since it occurs very rarely as a result of stimulation here, although somatic sensation in the tongue is the most frequent sensory response in the face area. (e) Intra-abdom-

inal sensation has been added to the lower end of the sequence, below throat. The extent of this representation, which is largely precentral, into the island of Reil has not yet been determined.

2. Sensory responses simultaneously in more than one of the area units of the face region are fairly frequent. The same is true among the units of the upper extremity. It is, however, very rare that overlap occurs between the three major regions — face, upper extremity, lower extremity. This may cast light on the fact demonstrated by Dusser de Barenne and McCulloch that each of these regions may be activated in animals by local application of strychnine without activating the adjacent major region.

3. Stimulation of the banks of the Rolandic fissure has shown that the sensory and motor responses produced there are similar in character and location to those elicited from the superficial surfaces of the pre- and postcentral gyri.

4. In the motor sequence certain minor alterations are also suggested. (a) Salivation and mastication are represented in the lower portion of the motor face area. The latter is predominantly postcentral in location and below tongue, whereas simple jaw movements are predominantly precentral in location and located above tongue. (b) Neck movements are represented between the area for finger movements and the upper margin of the face area.

5. Vocalization may be produced in man from an area between upper face and throat of both the dominant and nondominant hemispheres, either alone or with movement or sensation in the various structures about or in the mouth.

6. Conjugate eye movements toward the opposite side are produced by stimulation anterior to the precentral gyrus without seeming to be confined to a discrete architectonic area. Eye movements produced from the precentral gyrus may be conjugate to either side or upward or may be movements of convergence. Eye sensation is produced by stimulation anterior to the central fissure but not posterior.

7. Evidence is presented for the possible existence of a second sensory area for arm and leg in the cortex adjacent to the fissure of Sylvius. It seems likely also that there may exist in the same zone a second representation of movement.

Secondary motor areas. As indicated in Rasmussen and Penfield's last paragraph, there is some suggestion that secondary sensory areas exist as Adrian⁷² and Woolsey⁷³ have indicated, but that there is also evidence of the existence of a secondary motor field. Speculations in this connection have indeed been rife for some time. Thus, in 1943 Garol⁷⁴ found a second motor area in the cat lying in the inferior portion of the anterior ectosylvian gyrus, and here the representation was inverted as compared with that of the first motor region, — that is, the leg area was more lateral than the arm and head, — just as Woolsey and Fairman⁷⁵ have found for the second sensory area of the cat and monkey.⁷⁶ French, Sugar and Chusid⁷⁷ find on strychninization of the buried opercular surface that it "fires" heavily into areas 4 and 6 and also into postcentral gyri. To quote these authors further

The arrangement of connections as found by strychnine neuronography agrees with the somatotopic arrangements found on sensory and motor explorations. Anterior segments of the superior Sylvian bank communicate more actively with the inferior portions of the pre- and postcentral gyri, while the more posterior segments of the infraparietal plane are more strongly connected with the superior portions of areas 4 and 1. The face region is thus predominantly anterior, and the leg region posterior, in the superior Sylvian bank — an arrangement which agrees well with the other studies.

The functional significance of these second sensory and motor areas is thus being effectively elucidated through the use of Dusser de Barenne's invaluable new technic of strychnine neuronography.

EXTRAPYRAMIDAL FUNCTIONS

The secondary motor areas described above belong strictly to the extrapyramidal division, but they have been grouped with the corticospinal system since normally they discharge principally through the pyramids. The interaction, however, between the pyramidal outflow and that of extrapyramidal projections from the cortex and from subcortical levels, is close-knit, and they are difficult to disassociate in the intact animal. Denny-Brown,⁶⁶ in his monumental treatise on the diseases of the basal ganglions and subthalamic nuclei, is the first clinical writer to give adequate attention to the part played by the cerebral cortex in genesis of symptoms of extrapyramidal disease, although Kinnier Wilson⁷⁸ had pointed the way.

The underlying mechanism of the so-called extrapyramidal syndromes, such as Parkinsonism, chorea and other hyperkinetic states, has been clarified during the past five years through experimental studies carried out on primate forms. The fact that the suppressor areas of the cerebral cortex — that is, areas 2s, 4s, 8s and 24 — operate by direct connection with the striate bodies and thence via the thalamus back to the cerebral cortex indicates that one cannot regard the extrapyramidal system as separate from the cerebral cortex. The suppressor bands in the chimpanzee are shown in Figure 5.

Many years ago Kinnier Wilson⁷⁸ insisted that the tremor of Parkinsonism must originate in the cerebral cortex through the operation of extrapyramidal projections unsupported by the striatum and subthalamic nuclei. Bucy⁷⁹ has offered the hypothesis that since the extrapyramidal suppressor bands operate through a circuit involving the striatum, thalamus and thalamocortical projections, interruption of that circuit at any point — be it the corticostriatal path, the caudate nucleus, globus pallidus, thalamus or the thalamocortical projection — may give rise to manifestations of Parkinsonism. This hypothesis harmonizes with the known variability of pathologic lesions in Parkinsonism. It does not, however, fully account for the fact that the substantia nigra and reticular formation are generally heavily involved in advanced Parkinsonism. Moreover, Ward, McCulloch and Magoun⁸⁰ find that the syndrome of tremor and rigidity, closely akin to Parkinsonism in man, can be precipitated experimentally in monkeys by Horsley-Clarke lesions involving the reticular formation throughout its entire length. Attempts to reproduce the syndromes in monkeys and chimpanzees by lesions of the striatum have been uniformly disappointing, and Ward's results strongly suggest that the vital lesion of Parkinsonism lies in the reticular formation. One of

Kennard and Fulton's⁸¹ chimpanzees showed marked athetoid movements following a lesion restricted to the globus pallidus, which indicates that athetosis and Parkinsonism are no doubt distinguishable in terms of basic mechanisms

Comparative studies of the type just outlined lend support to the view that many of the extrapyramidal syndromes that occur in human beings are probably peculiar to the human nervous system. It has been impossible, for example, to cause anything remotely approaching chorea or athetosis in a dog or a cat. In monkeys states similar to chorea in man have been seen, and in the chimpanzee present indications are that one may be able through isolated destruction of the individual extrapyramidal nuclei to evoke many more of the clinical extrapyramidal syndromes

Applications

Relief of hyperkinetic states The therapeutic uses to which the newer knowledge of cerebral function may be put have begun to be dimly appreciated, but the wider applications are undoubtedly in their earliest developmental stages. Parkinson,⁸² in his celebrated essay on the shaking palsy, observed in 1817 that tremor of long standing disappeared after a hemiplegia, many similar instances of tremor vanishing subsequent to a stroke can be culled from the clinical literature. In 1909 Horsley⁸³ removed the arm area of a fourteen-year-old boy who had had severe unilateral athetosis for seven years, the patient's athetoid movements were completely suppressed after the ablation, and they continued so for a year (when the patient had been last examined). It is incidentally interesting that the patient suffered a severe flaccid paralysis as a result of the ablation, but this seems not to have made an enduring impression upon the neurologists who had examined the case.

With the revival of interest in functional localization in the cerebral cortex neurosurgeons, especially Bucy and Buchanan,⁸⁴ Bucy⁸⁵ and Sachs,⁸⁶ have lately begun to make cortical ablations for the relief of focal seizures (in which the results have been for the most part excellent), and also for the relief of hyperkinetic states—choreoathetosis, hemiballismus, torsion spasm and so forth. Opinion, however, has been divided regarding whether ablations of area 6 or of area 4 are the more effective. It is Bucy's contention that the involuntary movements of chorea and athetosis arise from premotor discharge via the pyramidal system. Klemme⁸⁷ shares a similar view concerning the origin of Parkinson tremor and favors premotor ablation since he believes it less debilitating from the motor standpoint. Bucy⁸⁸ has recently reported upon a striking case of unilateral weakness and athetosis that had persisted for fifteen years in a twenty-three-year-old man. After isolated ablation of area 4, tremor was completely and permanently abolished, and

although the patient suffered considerable paresis and excessive sweating in the affected extremity, the relief from his tremor proved particularly dramatic.

Suppressor areas in man It is of primary significance that Garol and Bucy,⁸⁹ in their patient from whom area 4 was ablated for the relief of tremor, were able positively to identify 4s, the suppressor band lying just rostral to the anterior margin of area 4 (Fig 9). On stimulation of this region, resting contraction of all muscles on the opposite side of the body was inhibited, the threshold for stimulation of area 4 itself was greatly increased, and the effect persisted for several minutes after stimulation. The observation is important, for it represents the first positive demonstration of the existence of a suppressor band in the human brain, the position of the band being closely similar to that of area 4s in the chimpanzee (Fig 10). This fact takes on fresh significance in the light of the recent study of Russell⁹⁰ on the relation of site of lesion to subsequent development of seizures in a series of cases of gunshot wounds of the brain.

Traumatic epilepsy Many who have had experience with gunshot injuries of the brain have noted the fact that some patients develop epileptic sequelae, whereas others—with seemingly similar wounds and with similar post-traumatic history—have failed to do so. Russell,⁹⁰ impressed with the possibility that the suppressor bands discovered by Hines⁹¹ (and brilliantly elucidated in the chimpanzee by Dusser de Barenne and McCulloch⁹²) have some causal relation to focal seizures, has plotted the site of injury in 138 cases of post-traumatic epilepsy and in 222 cases in which convulsions had not developed eighteen months to three years after wounding. The sites of wounding in the epileptic cases tended to accumulate in certain zones that correspond closely to the position of the suppressor bands as worked out in the chimpanzee. Little is known as yet concerning the actual position of the suppressor areas in man (except for the observation of Garol and Bucy⁸⁹ on area 4s), but there is every reason to suppose that they correspond to those in the chimpanzee. These important findings suggest that destruction of a suppressor band would release epileptogenic foci from inhibitory control and so precipitate seizures. Russell has put forward his findings with the greatest modesty, but many are prepared to believe that he has made a discovery of outstanding significance to neurology.

THE CEREBELLUM

The advances in knowledge of frontal-lobe function parallel those concerned with the cerebellum. Thanks to the work of Larsell⁹³ and Dow,⁹⁴ the cerebellum has emerged as a tripartite organ with discrete functional localization in three major spheres of integration: equilibration in the flocculonodular lobe, postural regulation in the anterior

hind extremity was stimulated, the primary responses appeared in the centralis. These studies were later considerably extended by Adrian,⁹⁶ who obtained the same pattern of reaction with lumbar and sacral segments having representation more anteriorly than thoracic and brachial segments

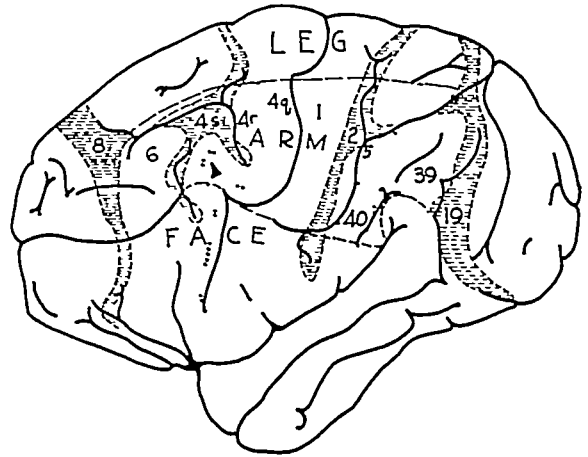
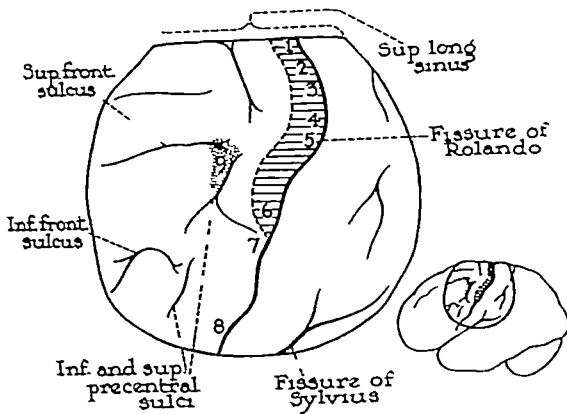


FIGURE 9 *The Suppressor Area 4s in the Human Cortex*
The stippled area 9 when stimulated caused generalized muscular relaxation, a rise in threshold of stimulation of points 1-8 in Area 4 and curtailment of after-discharge of area 4 response. The shaded area shows the strip of area 4 that was subsequently ablated 1—flexion of the right hip, 2—contraction of the right quadriceps femoris muscle, 3—contraction of the right pectoralis major muscle, 4—flexion of the fingers of the right hand, 5—flexion of the right elbow and wrist, 6—movement of the neck and right shoulder, 7—movement of the right corner of the mouth and contraction of the right platysma myoides muscle, 8—movement of the lower lip on the right side, and 9—suppressor area (area 4s) (Reproduced from Bucy⁴¹ with the permission of the publishers)

[illegible]

FIGURE 10 *The Suppressor Areas in the Chimpanzee*
 Map indicates areas of sensory and adjacent cortex, distinguishable by physiologic neuroanography, in *Macaca mulatta* (a) and *Pan satyrus* (b) Below are diagrams indicating maximal axonal field disclosed by repeated strychninizations in area marked Δ Horizontal dashes indicate suppression of electrical activity, Y indicates area fired, ce refers to central sulcus, double vertical lines indicate anterior and posterior borders of sensory cortex (Reproduced from McCulloch, [Chapter VIII] in Bucy,⁵⁵ p 233, with the permission of the publishers)

sends to and receives fibers from the vestibular nuclei. The anterior lobe receives the spinocerebellar projection and sends motor bundles to the reticular formation, red nucleus and other levels of extrapyramidal motor function, the posterior lobe receives its primary input from the frontopontocerebellar projections arising in the cerebral cortex.

Beyond these large primary divisions there has been until recently little evidence of more precise functional localization. Focal lesions, to be sure, had been made, both in the posterior and in the anterior lobe, but the resulting deficits never appeared to be sharply restricted to a given muscle group, or even to a given extremity. The only localization that was recognized was that the right half of the cerebellum presided over the homolateral musculature and the left over the musculature on its side. The first suggestion of more precise functional localization came from study of action potentials led off from the cerebellar cortex by Snider and Stowell⁹⁵. They found, when the upper extremity was stimulated, that well developed action potentials appeared in the culmen, whereas when the

The face, similarly, had representation more posteriorly in the posterior culmen and lobulus simplex. Adrian⁹⁷ made the interesting observation that the pig, which so largely depends upon its nose for its food supply, has a relatively enormous representation of its snout in sensory cortex.

The problem of functional localization in the anterior cerebellum has also been approached by

two other methods — namely, focal ablation and combined cortical and cerebellar stimulation. The ablation studies, which were begun by Connor⁹⁸ in 1940-41, gave unsatisfactory evidence, for although there appeared to be, in the dog at least, fairly clear evidence of functional localization, the effects were seldom sharply confined to a single extremity, and he was at first under the impression that such localization as appeared to exist was in the reverse sequence of that indicated by the electrical studies of Snider and Stowell. In an effort to obtain more satisfactory evidence of focal lesions, Soriano and Fulton⁹⁹ used the device of removing areas 4 and 6 from the cortex (monkeys) at a first operation (which gave a moderate degree of spasticity in both extremities of the opposite side). A focal lesion was then made in either the centralis or the culmen of the anterior cerebellum. When the lesion was in the centralis, the hind extremity became noticeably more rigid and more awkward than the upper extremity, when the focal lesion was restricted to the culmen, the reverse was true—that is, the upper extremity showed the most conspicuous effect.

Much more satisfactory, however, were the combined corticocerebellar-stimulation studies carried out by Nulsen and his associates¹⁰⁰. Nulsen had been influenced by the report from Hampson, Harrison and Woolsey¹⁰¹ that primary stimulation of the anterior lobe appeared to show evidence of localization similar to that disclosed by Snider and Stowell. Nulsen et al found that a cortically induced movement of a given extremity, such as the thumb, could be inhibited from a sharply defined focus on the anterior cerebellum and that a cortically induced movement of another muscle could be inhibited from another highly discrete focus. On mapping the cerebellum after this procedure, Nulsen was led to conclude that a degree of localization almost as sharp as that in the motor cortex itself exists in the anterior cerebellum and that a homunculus illustrating this generalization can be properly drawn. His summary was as follows:

Utilization of the inhibitory effect of cerebellar stimulation upon existing motor activity has permitted mapping of the anterior cerebellum as an homunculus representing individual muscles. The cerebral motor cortex or bulbar pyramid are stimulated at regular intervals and the uniform contractions of a single muscle are recorded. Simultaneous stimulation of cerebellar points is then undertaken to establish the location most effective for inhibition of response in that muscle. Such studies in the cat, dog, monkey, and chimpanzee under dial anesthesia show that the point corresponding to tail, hind-limb, fore-limb, and face musculature have an anteroposterior arrangement in lingula, centralis, culmen, and simplex lobules, respectively. Further localization in the monkey indicates that proximal muscles, as those of the upper arm, are best inhibited by ipsilateral cerebellar points near the mid-line, whereas distal muscles, such as the adductor pollicis, are best modified by lateral points in the same lobule. The homunculus for efferent effects thus obtained corresponds to that evolved by Snider and Stowell by observing the localized electrical activity of the cerebellar cortex induced by tactile stimulation.

In each animal, excepting the cat, increasing the frequency of cerebellar stimulation will result in facilitation rather than inhibition of the existing motor movement. The cerebellar homunculus for such facilitation is identical to that obtained when working with inhibition at low frequencies. The dentate nucleus (probably the dorsomedial portion) is involved in inhibition since its bilateral destruction allows only facilitation on surface stimulation, while its direct stimulation yields pure inhibition at all frequencies. Parallel evidence indicates that the fastigial nuclei transmit facilitatory impulses. Analysis of the effects of additional lesions of the brain-stem and cerebellar peduncles, combined with the oscillographic evidence of Snider, Magoun, and McCulloch, suggests that both inhibition and facilitation are ultimately mediated through the bulbar reticular formation.

Thus the same cerebellar point which receives tactile stimuli from a localized somatic area will upon electrical stimulation modify motor activity in the same region of the body. Depending upon the frequency of the stimulus, either inhibition or facilitation can be elicited from the same surface point. Evidence suggests that the pathways for the two effects then diverge to travel through different roof nuclei into the suppressor and facilitatory areas of the reticular formation. It is possible that these results of electrical stimulation may mimic the mechanisms by which the anterior cerebellum modifies the movements of an extremity in response to afferent impulses.

If the anterior cerebellum has given up some of its secrets, one can make an even more substantial claim for the flocculonodular lobe, for the war investigations of Bard et al¹⁰² have disclosed that ablation of this ancient nucleus (and of no other part of the forebrain) confers dramatic protection against motion sickness. Bard finds that dogs, whose susceptibility to vomiting when placed in a swing has been carefully appraised, continue to vomit after removal of any part or all of both cerebral hemispheres, even decerebration does not alter their susceptibility to swing sickness. The anterior and posterior lobes of the cerebellum can similarly be removed without effect, but if the nodulus is taken out in an otherwise unaltered animal, it can be swung for indefinite periods without signs of nausea and without the appearance of vomiting. The academic importance of this disclosure is, of course, considerable, whether my neurosurgical colleagues will take advantage of it in dealing with less seaworthy subjects remains an open question.

333 Cedar Street

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 35231

PRESENTATION OF CASE

First admission. A sixty-five-year-old man, a newspaper editor, entered the hospital with the chief complaint of chest pain of three and a half hours' duration.

The patient had been entirely well until about ten days before admission, when he noted for the first time some substernal pain. This first attack came on after his noon meal, while he was walking, lasted two or three minutes and was characterized as a dull, aching, substernal, nonradiating pain. Since then he had about one mild similar episode each day, usually coming on after eating or walking. On the morning of admission, while working at his desk, the patient again noted the onset of a substernal and precordial pain. This increased in se-

verity over three quarters of an hour. This time the pain was of constant, severe nature in the left chest and precordium, without further radiation. The patient began to sweat and went into mild peripheral circulatory collapse. A physician admitted him to the hospital two hours after the onset.

The past history was noncontributory.

Physical examination revealed a well developed and well nourished man in mild discomfort. There were no other significant abnormalities.

The urine had a specific gravity of 1.016, with a + test for albumin, and the sediment contained 5 white cells per high-power field. The white-cell count was 20,800, with 72 per cent neutrophils. The hemoglobin was 15.1 gm. A blood sedimentation rate was 13 mm per hour. An electrocardiogram showed findings consistent with a recent anterior myocardial infarct.

The patient was given quinidine sulfate and dicumarol. The prothrombin time was maintained throughout the hospital stay at an average level of about 35 per cent of normal. The white-cell count remained distinctly elevated, with figures of 20,800, 19,400, 16,000, and at the time of discharge 12,300. The patient stayed in the hospital five weeks. His hospital course was relatively uneventful. He continued to sweat profusely at times. Three weeks after admission he had an episode of profuse sweating, with discomfort in his epigastrium, which came on after lunch, lasted about ten minutes and then disappeared. There was no real pain associated with this. There was no other change in his physical

signs, and there was no recurrence of these symptoms. He was discharged at the end of five weeks.

Final admission (two months later) After leaving the hospital, the patient continued to do well, and he gradually arrived at the state where he could be up and around his home on one floor most of the day, with short rest periods and without symptoms. About five weeks after discharge, however, he began to have some paroxysmal dyspnea and orthopnea. He was digitalized and temporarily relieved, but because of increasing dyspnea in spite of digitalization, he was readmitted to the hospital.

Physical examination showed a pale and apprehensive man with distended neck veins. There were scattered rales, dullness and diminished breath sounds at both bases. Tactile and vocal fremitus at the right base was diminished. The heart was enlarged, the sounds were slightly diminished, and there was a protodiastolic gallop. The liver edge was percussed 2 cm below the costal margin. The prostate was symmetrically enlarged. There was no peripheral edema.

The temperature was 99°F, the pulse 92, and the respirations 24. The blood pressure was 170 systolic, 90 diastolic.

There was no change in the urinary finding from the previous admission. The white-cell count was 19,000, with 84 per cent neutrophils. The hemoglobin was 13.4 gm. The nonprotein nitrogen was 27 mg per 100 cc. The chloride was 86 milliequiv, the carbon dioxide 33.7 milliequiv, and the sodium 133.9 milliequiv per liter. An electrocardiogram was consistent with a healing anterior myocardial infarct. X-ray examination of the chest showed cardiac enlargement, both to the right and to the left. There was bilateral pulmonary edema, and a moderate pleural accumulation on the right.

In spite of intensive therapy, including full digitalization, mercurial diuretics, a low sodium regime and oxygen therapy, the patient remained in congestive heart failure, with recurring episodes of pulmonary edema that were very nearly fatal for a period of almost two weeks. A venesection produced some temporary improvement. The patient was febrile, the temperature being elevated to 102°F by rectum for the first week. On the third hospital day he was started on penicillin (300,000 units a day), and the temperature returned to normal three days later. Penicillin was discontinued on the tenth day. The patient developed acute urinary retention when he was first admitted, and this necessitated placing him on constant bladder drainage. In addition to digitoxin, penicillin and aminophyllin, quinidine was added as part of the therapy because of cardiac irregularities. The abdomen was very distended and tympanitic, and the patient gradually accumulated fluid in the right chest. In the face of strenuous and heroic therapy, he gradually improved. The lungs became less congested. The pitting edema of the thighs and sacrum, which de-

veloped soon after admission, had subsided by the tenth hospital day.

The laboratory data about the tenth hospital day revealed a hemoglobin of 9.5 gm, a white-cell count of 18,000, a normal urine, a nonprotein nitrogen of 31 mg, and a serum protein of 6 gm per 100 cc, a sodium of 133.6 milliequiv, a chloride of 82 milliequiv and a carbon dioxide of 31.5 milliequiv per liter. At the end of two weeks right-sided heart failure recurred as manifested by increasing distention of his neck veins, increasing fluid in his right chest, enlargement of the liver and marked distention of the abdomen. A chest x-ray film showed no change. Because of increasing difficulty in breathing and discomfort in the right chest a thoracentesis was done, yielding 1000 cc of clear, straw-colored fluid. This procedure afforded considerable relief of symptoms.

On the nineteenth hospital day, he began complaining of epigastric fullness, discomfort and hiccups. There was abdominal distention, most marked in the epigastrium. There was no spasm or tenderness. The abdomen was tympanitic. Stomach and rectal lavage was done, relieving the abdominal discomfort somewhat. The temperature, which had been normal, began to spike to levels of 101-102°F. Coincident with this last episode he became drowsy, lethargic and occasionally disoriented. The sodium was 119.1 milliequiv, chloride 82 milliequiv, and carbon dioxide 27.1 milliequiv per liter. The nonprotein nitrogen was 32 mg per 100 cc. He was given measured quantities of sodium chloride, crysticillin and sulfadiazine. His mental condition improved, but the fever and white-cell count of 22,000 continued. A urine culture showed colon bacilli and rare beta-hemolytic streptococci. After a week on crysticillin and a week on sulfadiazine without any effect on the temperature, streptomycin was started in dosage of 2 gm a day. Six days later his temperature returned to normal and remained so until the last thirty-six hours of his admission. He maintained this status for about two weeks. The striking features at this time were apathy, weakness, persistent anemia and leukocytosis. A rounded nontender mass was palpated far laterally in the right abdomen, just above the iliac crest. Several thoracenteses were done on the right, which always yielded clear, straw-colored fluid with 53 polymorphonuclear leukocytes, 21 lymphocytes and 125 red cells per cubic millimeter. No organisms were present in a smear and none were grown out in culture. After about forty days in the hospital his circulation was much improved. His congestion was in abeyance, but he remained weak, apathetic and gaunt in appearance. There was fluid at the right base, with a widespread friction rub over most of the right chest. The latter finding was a new development. A chest x-ray film at this time revealed that there was considerable decrease in the congestive changes previously noted.

in the lung fields. There was, however, still some prominence of the peripheral vessels bilaterally, and there may have been a minute amount of residual fluid at the right base. An anteroposterior view of the upper abdomen showed the right liver edge to be rather low in position.

Shortly after this the patient began to complain of some difficulty in swallowing. This was rather persistent. It was most commonly associated with the ingestion of pills. It was described as discomfort beneath the lower third of the sternum and under the right lower ribs. This sometimes seemed to be relieved by gelusil and at other times subsided spontaneously. These symptoms were persistent enough so that after two months of hospitalization, in spite of the patient's precarious position, a gastrointestinal series was done. He was examined in the recumbent posture and with only a minimal amount of time spent because of his cardiac status. There was no gross evidence of involvement of the esophagus, stomach or duodenum. About three weeks after the onset of difficulty in swallowing the patient began having intermittent attacks of right-upper-quadrant discomfort radiating laterally. This was frequently accentuated by deep breathing. Pain was only transitory, however, and was relieved spontaneously. The patient again associated the onset of this pain with the ingestion of the pills that he was taking. A complete physical examination at this time revealed fluid in the right chest, and some coarse, moist rales at the right base. The left chest was clear and resonant. The heart sounds were not changed. The abdomen was soft and flat. The liver was palpable, as was the rounded mass in the right lateral quadrant. It was still not clear whether this mass was a part of the liver or a separate entity.

On the seventy-sixth hospital day, while sitting up in a chair in his room and within a few minutes after swallowing two pills of enteric-coated sodium chloride, the patient complained of severe, excruciating pain in the upper mid-abdomen radiating toward the right lower costal margin. This pain increased in severity. The patient became cold and sweaty. The blood pressure was 150 systolic, 90 diastolic, the pulse 90 and regular, the respirations 25, and the temperature 99°F. The neck veins were flat, and the lungs were normal except for dullness at the right base. The heart sounds were not changed. The abdomen was rigid, particularly in the upper half. Peristalsis was absent. The pain was made worse by the supine position and was relieved by sitting up. Respiratory excursion was limited by the pain. The femoral pulses were normal. The white-cell count was 31,600, with 75 per cent neutrophils. The serum amylase was 33 units. Signs of peripheral collapse became more apparent. A plain film of the abdomen in the supine and upright positions revealed no air under the diaphragm.

An exploratory laparotomy disclosed no abnormalities in the stomach, biliary tract or small or large intestine. For the first twenty-four hours the patient rallied from operation with surprising stamina. The abdominal pain was relieved. He complained of some sharp pain in the left axilla aggravated by breathing. He was alert and in good spirits. The temperature rose to 102°F, and the pulse and respirations became more rapid. Thirty-six hours later, he began to fail. The pulse became weak and thready, and the respirations increased, the temperature rose to 106°F. There were absent breath sounds and diminished resonance over the entire left chest. There were no rales. The heart sounds were of good quality, but the rhythm was grossly irregular. The blood pressure was 140 systolic, 60 diastolic. The abdomen was soft and not distended. He died about forty hours after operation.

DIFFERENTIAL DIAGNOSIS

DR EDWARD D CHURCHILL. The first admission seems to have been an episode of myocardial infarction. The history is quite typical. The patient was brought into the hospital and stayed five weeks, and the infarction was confirmed by electrocardiographic findings — in fact, localized as a recent anterior myocardial infarct. I see nothing in the first admission that is not fully accounted for by that diagnosis, which apparently was the discharge diagnosis. It might be well to note that the white-cell count is recorded as 20,800, in association with this lesion. He was able to be up and around his home for about two months, and then the dyspnea increased and was uncontrolled by digitalization. The second hospital stay was a very long one, in fact, the terminal events started on the seventy-sixth day of residence. The former diagnosis of anterior myocardial infarction was confirmed by electrocardiogram, and the lesion was classified as "healing." The heart was enlarged, both to the right and to the left. There was bilateral pulmonary edema, and pleural effusion on the right. Venesection and a low sodium regimen appear to have been indicated, and apparently the situation was assayed as congestive heart failure with recurring episodes of pulmonary edema. Some of these were serious, since it is stated that only strenuous and heroic therapy finally led to improvement. The patient showed anemia and a hemoglobin of 9.5 gm and still had an elevated white-cell count. The kidney function seems to have been satisfactory. The venous pressure was elevated, and the chest was aspirated several times.

During the second admission, increasing abdominal symptomatology was apparent. On the nineteenth day, he complained of epigastric fullness, discomfort and hiccups, with abdominal distention. The leukocytosis and fever appeared to center on a secondary infection, and colon bacilli and beta-hemolytic streptococci were cultured from the urine.

He was treated with sulfonamides and finally streptomycin, and the fever subsided and remained normal until the terminal event. This was puzzling to the medical attendants as shown by the sentence "The striking features [even when the temperature was brought down to normal] were apathy, weakness, persistent anemia and leukocytosis." Then the observation was made that a round, nontender mass could be palpated far laterally in the right abdomen, just above the iliac crest—in other words, in the region of the appendix. That completes the grouping of a series of findings that pointed to something below the diaphragm. Previously, everything was associated with myocardial insufficiency and myocardial infarction. At this point, it is noted that a few days later a widespread friction rub was heard over the right chest. That was a new development, and came despite the fact that the pulmonary congestion was diminishing. A mass in the right lower quadrant, a friction rub over the right chest and persistent leukocytosis immediately raise the question, Did this man, during a period of cardiac decompensation, insidiously develop an appendiceal abscess with extension to the subphrenic space? Perhaps the fluid in the right chest is not explainable on the basis of cardiac decompensation. It may have been inflammatory. The fluid itself, taken from the right side, was clear and straw colored but did show 53 per cent polymorphonuclear leukocytes per cubic millimeter and remained sterile. It would be perfectly consistent with an inflammatory fluid in contrast to that from passive congestion. So I have no doubt that the constellation of events caused worry and discussion, because a man of sixty-five will sometimes, right under our eyes on a ward, develop an appendiceal abscess, showing very little reaction. Certainly, that is one of the first things that a palpable mass in the right lower quadrant suggests. There are many other happenings that could have caused the fluid in the right chest in addition to cardiac failure. Pulmonary infarction would have accounted for this completely, but I take it that there was no evidence by x-ray film of pulmonary infarction, in fact, the radiologist says that the lungs looked clearer than they had for two weeks.

Then a new symptom appeared—difficulty in swallowing, particularly noticed in swallowing pills. There was also discomfort below the lower third of the sternum and under the right lower ribs. I take it that this was intermittent but persistent enough, so that despite the fact that the patient was very sick he was taken to the x-ray department for investigation. A great many reservations were made about the findings. It is stated that the patient was examined in the supine position. Obviously, he was very ill, and the roentgenologists want us to know that they did not have complete confidence in the results of the examination. Dr Wyman will comment later. The abdominal symp-

toms again come to the fore. After about three weeks with the difficulty in swallowing, there began to be right-upper-quadrant discomfort radiating laterally, not very severe, apparently, or very disturbing to the patient. Again, it was the pills that were annoying him and seemed to bring on right-upper quadrant pain. Still no explanation was found. The liver edge was down, as one would expect with cardiac failure, with peripheral congestion and high venous pressure. The rounded mass in the right lower quadrant was still palpable. Again, reservations are thrown in—the examiners were not sure whether it was liver or a separate mass, although the story does not quite hang together, the liver edge was described as palpable just below the costal margin, and the mass was at the iliac crest.

An acute episode ushered in the terminal event on the seventy-sixth hospital day. The patient was sitting up in a chair in his room when he was given some more pills (enteric-coated sodium chloride). Severe, excruciating pain was felt in the upper mid-abdomen, radiating again toward the right and along the costal margin. This pain was more severe than any he had had before, and was followed by peripheral vascular collapse. The abdomen is described as being rigid, particularly in the upper portion. Peristalsis was audible, and he was much more comfortable while sitting up than when trying to lie down. Respiratory excursions were limited by pain. Apparently, his physicians worried about embolism and carefully ascertained, as far as the femoral arteries were concerned, that the circulatory pathways were not blocked. The white-cell count was high, but this was always a fairly constant finding in this case. Peripheral collapse was not severe at the onset because he was running a blood pressure of 150 systolic, 90 diastolic, and a pulse of 90, but it increased, and he was examined for a perforated viscus by inspection for air under the diaphragm. Operation was performed, apparently in the belief that an acute abdominal crisis had occurred. Lo and behold, no disease was found at operation! It is definitely stated that there were no abnormalities in the stomach or biliary tract or in the small or large intestine. If we accept that statement at its face value, we must rule out the tentative diagnosis of appendiceal abscess. So, I see no justification in entertaining the somewhat attractive idea that this man had a smoldering appendix with subphrenic-space infection. Certainly exploration during life is nearly as accurate as exploration at autopsy, and we have to keep on the beam of the evidence as given to us. After the operation, the examiners appear to have been somewhat surprised that the patient staged a comeback and complained no longer of abdominal pain. Perhaps he had medication, or other ancillary treatment, and forgot about it, but he had other events to worry about. A sharp pain appeared in the left

axilla and was described as pleuritic. The pulse and respirations were more rapid. He then went into a tailspin of peripheral vascular collapse, the temperature rising to 106°F. There were terminal atelectasis and aspiration pneumonia, presumably, of the left lung associated with pleuritis, completely irregular cardiac rhythm and death forty hours after operation.

Dr. Wyman, will you give any x-ray evidence that you have on this obscure case?

Dr. STANLEY M. WYMAN: The first two films taken at the first admission show bilateral pleural effusion. The heart is large but without characteristic configuration. There is rather pronounced engorgement of the hilar and pulmonary vascular shadows. The next film, taken a month later, shows what is probably a large collection of fluid in the right pleural space and a hazy ground-glass density overlying both lung fields centrally, consistent with edema. A little more than three weeks later the lung fields have cleared very definitely, and the fluid in the right pleural space also appears to have decreased considerably. Taken on the same day is this film of the upper abdomen.

Dr. CHURCHILL: This is at the time he was sent down in a search for a cause of the difficulty in swallowing?

Dr. WYMAN: No, this is a month before that. This film shows the liver margin extending down close to the iliac crest.

Dr. CHURCHILL: Could that have been the mass that was felt?

Dr. WYMAN: I should think so, but I should think the tip of the liver would have been recognized.

Dr. CHURCHILL: The examiners did not know whether it was liver or not.

Dr. WYMAN: There is nothing particularly diagnostic on these films. This is the film after barium was given in an attempt to explain the difficulty in swallowing. It shows no gross abnormality in contour or position of the lower esophagus, stomach or duodenum. The next films are taken approximately a month later, and the liver shadow appears to have increased in size still further and is now overlying the upper portion of the right ileum. I do not recognize any definite bone metastases or any abnormal soft-tissue shadows. The kidney outlines are fairly well seen.

Dr. DANIEL S. ELLIS: What is the shadow overlying the eighth dorsal vertebra?

Dr. WYMAN: I think that is an artifact. It may well be a pill.

Dr. CHURCHILL: In doing the fluoroscopy, did they get a look at the full length of the esophagus?

Dr. WYMAN: I would assume so from the description. I believe the fluoroscopist probably had his best look at the esophagus. That usually is the case in a gastrointestinal series on a person as sick as this. One can see the esophagus quite well. It is more difficult to see the stomach and duodenum.

Dr. CHURCHILL: But you do not see any x-ray evidence of, let us say, cancer of the esophagus obstructing the swallowing of pills?

Dr. WYMAN: The only evidence is the fluoroscopist's word. There is no evidence for or against it on the film.

Dr. ELLIS: How much fluid is there in the left chest?

Dr. WYMAN: The film was taken with the patient lying down, and I can see no evidence except a small quantity in the costophrenic sinus. I think he had a small amount. There may be more posteriorly, which I cannot see.

Dr. CHURCHILL: There is one major question we might as well try to resolve on the evidence. Did this man have intra-abdominal disease? What kind of intra-abdominal disease could be overlooked at a laparotomy forty hours before the patient died of it? It seems to me that we have to follow the record here. It is stated that there were no abnormalities in the biliary tract. Does that include the liver?

Dr. ELLIS: It was an entirely negative exploration except for slight congestion and enlargement of the liver.

Dr. CHURCHILL: Otherwise nothing was seen or felt in the abdomen?

Dr. ELLIS: That is right.

Dr. CHURCHILL: He was operated on within a few hours of the episode of collapse?

Dr. ELLIS: Four hours.

Dr. CHURCHILL: There is one question we should ask ourselves. Could a mesenteric thrombosis or an occlusion of the celiac axis have been present without changes visible to or palpable by the surgeon four hours after it occurred? I should think not. A lesion of the mesenteric vessels that causes death in forty hours would show some dusky or lack of pulsation in the mesenteric arteries at four hours. So it seems to me, as the evidence stands, that we must accept the physical findings of laparotomy as ruling out the acute abdominal crises that may be expected to occur with hypertensive cardiac failure. We must also rule out completely the somewhat tempting idea of appendiceal abscess, with liver or subphrenic-space abscess, because the surgeon in exploring this man would certainly run his hand up over the dome of the liver. We must also rule out perforated viscus, volvulus and other acute abdominal emergencies.

We then come to a discussion of acute and fatal episodes that might be linked with the difficulty in swallowing and cause pain, excruciating in nature, in the epigastrium. There is one very rare entity—namely, rupture of the esophagus. With rupture of the esophagus all the signs and symptoms of an acute abdominal emergency may be present, and abdominal exploration if carried out will be negative. Is it possible that when swallowing these large pills the patient tore the lower end of his esoph-

agus? Cases of rupture of the lower thoracic esophagus, as I say, are rare, but they have been diagnosed occasionally in life. It seems to me that we are left with that as the one possible solution. Was this rupture of a normal esophagus or extension of infection by trauma to an ulcer of the esophagus or perforation of cancer of the esophagus? It seems to me that we have to accept the findings of the fluoroscopist that there was no cancer of the esophagus causing obstruction to swallowing. However, he might have overlooked a small ulcer. Things happened so rapidly at the end and were so characteristic of an acute emergency that it does not seem possible to say that the patient died of another myocardial infarction. The heart sounds were of good quality, although the rhythm was grossly irregular.

The only suggestion I have to offer from the surgical point of view is that of rupture of the lower thoracic esophagus. It could have proved fatal in about forty hours and not have been disclosed at laparotomy. I will leave to Dr. Ellis whether the terminal event here could be interpreted simply as another major myocardial infarction. Obviously, the medical attendants did not think so, or they would not have called the surgeons to operate.

DR. BENJAMIN CASTLEMAN: How do you account for the chronic abdominal pain?

DR. CHURCHILL: I do not account for it.

DR. CASTLEMAN: It would have nothing to do with the final diagnosis?

DR. CHURCHILL: I would like to account for it, but with a completely negative examination of the abdomen by laparotomy a few hours before death I do not believe one has any basis to account for it.

DR. ELLIS: The protocol was as complete as we could make it, so I have very little to add. In retrospect, I think that some of the discomfort in the right chest, which we had been attributing purely to encroachment on the lung by fluid, may have been due to something else. On the other hand every time we tapped the right chest the patient was relieved of the discomfort. With regard to the cell count of the chest fluid, though leukocytes were present there were never many cells, and we had no idea that anything else was going on other than right hydrothorax, on the basis of cardiac failure. No further cell counts were done until after the third tap, which showed a negative culture.

The mass described was thought by one examiner at one time to be the liver and at another time a separate entity. The uncertainty was caused by the abdominal distention. I personally came to believe that it was a long tongue of liver extending down laterally and was a part of the liver and probably not any other mass.

As far as the terminal episode is concerned, with the negative exploration we were just as much puzzled

as Dr. Churchill. We, of course, considered the possibility, as we had done before operation, that the episode was caused by another myocardial infarct, but we ruled that out because the heart sounds remained good and the electrocardiogram the next day showed no further evidence for infarction. I believe that the terminal picture was due as much to a massive collapse of the left lung superimposed on his weakened myocardium as anything else. The temperature of 106°F pointed to a superimposed element of infection. But I doubt very much if this patient could have survived the massive collapse and everything else he had. That was the thing that tipped the picture if he did not have massive collapse I doubt if he would have died as soon as he did. I would like to ask Dr. Churchill if perforation of the esophagus could have occurred forty hours before death. If so, how does he explain the anemia, the persistent white count from the time of admission and the weight loss?

DR. TRACY B. MALLORY: Can you go any farther, Dr. Churchill?

DR. CHURCHILL: I cannot explain past events because I am accepting verbatim the completely negative findings in the abdomen. There are many unexplained features in this case. I see no group of symptoms, however, or findings that point toward any other specific diagnosis.

DR. ELLIS: I might say that we operated with a diagnosis of perforated peptic ulcer and thought that was what we were dealing with.

CLINICAL DIAGNOSES

Massive collapse, left lung
Myocardial infarct, with congestive heart failure
Dissecting aortic aneurysm?

DR. CHURCHILL'S DIAGNOSES

Perforation of thoracic esophagus, with mediastinitis and pleuritis
Old myocardial infarction
Hypertensive heart disease, with cardiac decompensation

ANATOMICAL DIAGNOSES

Ulcer of esophagus, with perforation into mediastinum and left pleural cavity
Subacute mediastinitis
Empyema, left, acute
Massive collapse, left lung
Coronary thrombosis, old
Myocardial infarct, old
Duodenal ulcer, active, penetrating

PATHOLOGICAL DISCUSSION

DR. MALLORY: I will show a lantern slide demonstrating the major finding, which Dr. Churchill

correctly predicted. There was a perforation of the esophagus, which can be seen at this point where the toothpick has been inserted through an orifice measuring 9 by 13 mm. We found nothing suggesting that there had been a diverticulum at that spot, and we do not see in the microscopical sections the evidence of peptic ulceration that one sometimes sees in esophageal perforation, so we cannot state what the etiology of the ulcer was. There was a considerable amount of purulent infiltration throughout the mediastinal tissues, which we classified as subacute. I am not able to give a very exact estimate of its duration. At the time of autopsy the ulcer communicated directly through into the left pleural cavity, and there was a very fresh empyema on the left. The mediastinitis was certainly of longer duration, so I would assume that the ulceration had occurred in two stages, an initial penetrative into the mediastinal tissues producing mediastinitis, and a second one, when the process broke through into the pleural cavity, which accounted for the terminal episode of collapse. There was an old myocardial infarct that had been correctly placed by electrocardiographic evidence and at the time of autopsy was completely fibrous and healed, with evidence of fresh extension. The left descending coronary artery showed completely occlusive organized thrombus. The mass in the right lower quadrant was an abnormal knob, which extended from the lower margin of the right lobe of the liver, simply an anomaly in the shape of the liver.

We did find one intra-abdominal condition that may have been responsible for a significant portion of the symptoms, a penetrating ulcer of the posterior wall of the duodenum backing up against the pancreas. It could certainly have been responsible for the anemia and for some of the pain. It is one of the easiest of intra-abdominal conditions to overlook at even a very careful exploratory operation.

DR ELLIS: The patient's stools were repeatedly guaiac negative.

DR JACOB LERMAN: I would like to suggest the possibility that some of the chronic abdominal pain was due to hypocalcemia and hyponatremia as is seen in Addison's disease for example.

DR MALLORY: The possibility I cannot rule out, although I think we have two adequate anatomic explanations for it.

DR CHURCHILL: I think the combination of a duodenal ulcer and an ulcer in the esophagus might have caused it. The ulcer of the duodenum was penetrating the head of the pancreas.

DR ELLIS: You do not think that the pills, the enteric-coated salt, had anything to do with perforating the esophagus, do you?

DR MALLORY: I would hate to be challenged in court on that.

CASE 35232

PRESENTATION OF CASE

First admission. A fifty-five-year-old single school-teacher was admitted to the hospital because of pain in the left flank.

One week before admission she awoke with severe pain in the left flank. The pain did not radiate and was steady. At the onset there were five loose bowel movements, but following this the bowels were normal. The bowel movements aggravated the pain. The pain remained severe for one day and then slowly diminished. She was admitted for study.

The temperature, pulse and respirations were normal. In the lower abdomen there was generalized tenderness most marked on the left. A tender mass was felt arising from the pelvis. A barium enema demonstrated multiple diverticula, most numerous in the region of the upper sigmoid, where there was marked spasm, there were streaks of barium extending outside the lumen of the bowel on its medial aspect. In the region of the gall bladder there were three ring shadows, which a Graham test proved to be in the gall bladder. The dye concentrated normally.

A gall bladder full of stones was removed. The common duct was explored and was normal. Convalescence was uneventful.

Second admission (ten years later). In the interval the patient remained on a low roughage diet and mineral oil. There was no change in bowel habit. She occasionally noticed an increased feeling of gaseousness, especially after eating, and this was often relieved by passing of gas or a bowel movement.

Five days before admission the patient was awakened by a sudden, severe pain in the left upper quadrant that spread across the abdomen. She

believed that passing gas might relieve the pain. She fainted twice and her doctor found a large mass in the left upper quadrant and severe left-costovertebral-angle tenderness. Several hours later the doctor found the mass to be smaller. There was no nausea. The pain subsided and did not recur. Bowel movements did not change during the days preceding admission and the appetite remained fair.

Physical examination of the heart and chest was negative. In the left upper quadrant there was a definite sense of increased resistance with a questionable, tender mass. There was spasm and some costovertebral-angle tenderness. Examination of the urine was negative.

The temperature, pulse and respirations were normal.

An intravenous pyelogram was reported as follows:

Preliminary films show a small patch of density adjacent to the superior aspect of the left pelvic aperture, which may represent barium outside the colon from a previous examination or is possibly still present in a diverticulum of the sigmoid. There is evidence of a mass in the left mid-abdomen, which is rather vaguely made out but appears to measure at least 10 cm. in its greatest dimension. The left psoas muscle is just visible through the density of the mass although it is not well defined. The inferior pole of the left kidney is likewise just barely visible. There is no definite evidence that the mass is associated with the kidney, although the likelihood is not entirely excluded. The opaque medium is excreted promptly by both kidneys in good concentration outlining essentially normal-appearing renal calyces, pelvis and ureters, except for a suggestion of slight displacement of the proximal left ureter medially. A barium enema shows multiple diverticula in the region of the sigmoid and a lesser number in the distal transverse and descending portion. There is evidence of encroachment by the mid-abdominal mass upon the descending colon and distal transverse colon.

A gastrointestinal series was negative except for a hiatus hernia. The body of the stomach and proximal jejunum were displaced toward the midline by the previously described mass. There was no evidence of splenic enlargement.

An operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. WALTER E. GARREY: The first admission seems to be a clear-cut story of a flare-up of diverticulitis of the sigmoid with perforation, apparently well walled off. During the course of interpreting these abdominal films three ring shadows were demon-

strated that were evidently gallstones. Some time later (I suppose time was allowed for the diverticulitis situation to improve), an operation was performed, and a gall bladder full of stones was removed. The surgeon evidently found small stones as well as large, round ones, and he explored the common duct and found that it was normal. That was over ten years before the second admission, so I suppose the films are not available. The patient had an uneventful convalescence and got along well for ten years.

Then she came back with a different story, at the age of sixty-five. She had been advised to maintain herself on a low roughage diet and had taken mineral oil. We are not told about leukocytosis or the total blood count and smear. Both were noncontributory, I judge, and I also judge that the temperature was normal during the period that followed entry.

There was x-ray evidence of encroachment by a large abdominal mass on the descending colon and the distal transverse colon. I hope for further amplification of the word "encroachment." I want to know if Dr. Wyman can see any evidence of mucosal involvement of the bowel itself by this mass or whether it really means that the position of the mass was such that it had altered the position of the transverse and the descending colon. I would particularly like to know whether any lateral films were taken, either during barium enema or lateral oblique films during the pyelogram.

May we see the x-ray films? I do not have much of a clinical story and I cannot feel the mass, so I have to depend a good deal on what help I can get from the x-ray studies.

DR. STANLEY M. WYMAN: The plain film of the abdomen as described in the protocol shows the indistinct border of the left psoas muscle. There is a sense of increased density overlying this area, which cannot be accurately outlined. The left kidney lies definitely lower than usual, and I think that this lower pole is more medially placed than the right and certainly more medially than is commonly seen. There is also some displacement of the upper ureter as suggested in the protocol. This is the area of unusual density described on the plain film, which was thought to be barium from previous examination. Three films of the barium enema show extensive diverticulosis in the sigmoid, descending colon, and distal transverse colon. The mass

lies in this area and appears to displace the colon without involving it. This film was taken with the left side raised in oblique projection, and shows that the mass lies well posteriorly. The two films from the upper gastrointestinal series show again a mass displacing loops of jejunum medially. I think there is a hiatus hernia but nothing more that I can be sure of. Incidentally, from the previous story I believe that this shadow of barium actually is a small extravasation adjacent to the colon.

DR GARREY: The x-ray studies have been helpful. From the protocol I certainly had no very clear idea whether we were dealing with an intraperitoneal mass or a retroperitoneal mass, and if a retroperitoneal mass whether or not it was extrarenal.

I think we can begin our discussion by eliminating certain possibilities that seem unlikely. I would eliminate first of all primary renal tumor on the basis that all the renal calyces are seen, and that there is no demonstrable distortion of any renal calyx. I would think, then, that, while we cannot be absolutely sure that this mass was not associated with structures near the root of the mesentery, the lateral film here suggests that it had its origin far posteriorly, and that it probably was a retroperitoneal mass, rather than a mass in the root of the mesentery. I would have liked to see, for a retroperitoneal tumor, a little more displacement or distortion of the kidney, either by rotation or by displacement of the ureter, than is demonstrated here, but, still, there apparently was some. I would eliminate any connection between this mass and the previous diverticulitis. I think it is unlikely that this mass had resulted from a perforation posteriorly. In the first place the diverticula are usually along the other border of the bowel. We are not told that she ran a temperature or leukocytosis. When we do come down to the question of what sort of retroperitoneal, extrarenal mass this might have been, there are legions of tumors that occur in this area. Many of them probably have their origin in the structures along the urogenital ridge and may have a variable histology. They may be embryonal-cell carcinoma or various tumors or may show mixed histology. This might be a fibroma or neurogenic sarcoma or fibrosarcoma. It seems to me too laterally placed to be derived from lymph-node structures, and I doubt that it was any of the malignant lymphoma series. Could it have originated from an adrenal rest or from the adrenal gland

itself? There are large adrenocortical tumors that are found in this retroperitoneal flank area, and they do not, by any means, show endocrine stigmas on the surface of the body. However, one would expect that the kidney would be displaced downward if this were adrenocortical carcinoma, and I think that is unlikely. Was this mass tender? Why did this patient have acute pain for a while? The best hypothesis, I think, is that in some way the encroachment of this mass on the bowel with narrowing of the bowel caused some transient distention of a hollow viscus even though she did not vomit, and the exacerbation of pain that came and went was on that basis.

I will venture to say that the operating surgeon was not very sure of exactly what kind of tumor he was going to find, or whether it could be extirpated and cured. I would like to know what the preoperative diagnosis was. I take it that no bruit was heard with a stethoscope in this mass and no pulsation made out, or such a finding would have been indicated in the protocol.

In summary, I would eliminate any infectious process and would eliminate aneurysm and would come back to a solid tumor, which I believe to be a retroperitoneal rather than an intraperitoneal one. But I would simply say that the exact histology of such a mass is usually not predictable until the time of biopsy or excision, but from the general shape of this thing one might expect it to be an embryonal-cell carcinoma or one of the spindle-cell tumors, neurogenic sarcoma or fibrosarcoma. I take it that the possibility of a secondary implant from something in the pelvis is pretty well ruled out by adequate pelvic or rectal examination, and in a woman, of course, the extremely common situation of metastasis from a small tumor in the testicle is eliminated.

DR CLAUDE E. WELCH: Dr. Wyman, is the shadow of the spleen discernible on the films?

DR WYMAN: I think it lies in this region, it is not remarkable.

I do believe, Dr. Garrey, that the left kidney lies lower than usual.

DR GARREY: That could bring us back to primary adrenal neoplasm, but it seems to me that the kidney is not displaced very far down. It is probably lower than the one on the right. It is rotated. That would be further evidence for a retroperitoneal extrarenal lesion. I would like to revise my assump-

tion and bring in another structure as a possibility, although I think it is unlikely — namely, something in the tail of the pancreas. It seems to me that the whole shape and delineation of this thing is down farther than a pancreatic cyst or tumor in the tail of the pancreas would be, and I am accepting the x-ray statement that the shadow of the spleen could be seen to rule out cyst of the spleen. I do not believe that would be nearly so likely to displace the kidney downward, and it brings me back to whether this might be an adrenal tumor or sympathicoblastoma originating in the adrenal area. I can only say that it is a possibility.

CLINICAL DIAGNOSIS

Retroperitoneal tumor

DR GARREY'S DIAGNOSIS

Left retroperitoneal extrarenal tumor, either embryonal-cell carcinoma or neurogenic sarcoma or fibrosarcoma

ANATOMICAL DIAGNOSIS

Perirenal hematoma

PATHOLOGICAL DISCUSSION

DR HOWARD ULFELDER. As Dr Garrey so wisely predicted, we contented ourselves with a preoperative diagnosis of retroperitoneal tumor and did not believe the evidence warranted being more specific than that, although I personally thought it might arise from the pancreas. This patient was explored through a transverse incision in the left upper quadrant directly over the mass. The peritoneal cavity was free of any abnormality. The descending colon was pushed forward and ran over a retroperitoneal tumor, which was about as large as a baseball. Palpation of this tumor showed that the peritoneum was freely movable over it, and

there were a number of large vessels crossing it. It seemed to be in continuity and inseparable from the left kidney. It was my impression that we were dealing with a tumor of the lower pole of the left kidney, and therefore the incision was extended laterally and upward to remove the distal portion of the tenth rib and expose the retroperitoneal space after incision of the diaphragm. This allowed easy dissection of the tumor and kidney as one mass, the ureter was transected well below it, and it was then completely free except for the pedicle. The renal vein was normal to palpation, we transected it just distal to the left ovarian vein. The renal artery was cut, and the mass removed in one specimen and sent to Dr Mallory.

DR TRACY B MALLORY. The specimen that reached the laboratory showed a kidney embedded in a very large amount of hemorrhagic perirenal fat. The kidney was absolutely normal. The surrounding fat showed multiple dissecting planes of hemorrhage all through it and a few small foci of early fat necrosis.

The diagnosis, I think, is still somewhat questionable. In a woman of sixty-five asymptomatic rupture of a retroperitoneal vessel is a good possibility. We have on many occasions seen apparent acute abdominal emergencies from rupture of the hypogastric artery, simulating closely an attack of acute appendicitis, and I think in all probability rupture of an unidentified vessel in the perirenal tissues was the source of this hematoma. An outside possibility might be pancreatitis at the extreme tail of the pancreas. That was suggested by the small foci of fat necrosis, but there was nothing else to suggest it in either the clinical history or the anatomical findings. I think apoplexy of an unidentified perirenal artery was probably the cause of her symptoms.

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THE ANNUAL MEETING

THE Massachusetts Medical Society has celebrated its one hundred and sixty-eighth consecutive annual meeting. The record may be mentioned with pardonable pride as unparalleled in this country, the New Jersey Society began its existence in 1766 but held no meetings from 1775 to 1781, when the country was otherwise engaged, and again suspended operations between 1795 and 1807. The total registration was 1454, of which 1230 were physicians.

The Council met on the evening of May 23 at the Hotel Sheraton, in Worcester, with an unusually large attendance. At this meeting three new sections were voted into existence: a section on psychiatry and neurology, one on ophthalmology and otolaryngology, and one on industrial health.

A considerable amount of business was dispatched during the course of the evening. The Executive

Committee was upheld in its disapproval of the annual registration of physicians, and a co-ordinating committee to work with the American Medical Association in publicizing the advantages of voluntary over compulsory health insurance was approved.

The fourteen proposals for improving the distribution of medical care, adopted on February 9 by the committees on Medical Economics and Public Relations, were earnestly discussed. Proposal 13, agreeing that the federal Government should "subsidize medical and nursing education, medical indigents, health and diagnostic centers, including mental, where not now adequate," was referred back to the committee for clarification. The remaining proposals were accepted with suitable modifications.

Under an amendment to the report of the Committee on Ethics and Discipline pertaining to a code of ethical conduct for physicians and institutions in their public relations, the appointment of a committee of five to draw up such a code was approved.

After debate the organization of not more than five pilot health-protection clinics in pivotal localities in the State as recommended by the Department of Public Health and the Committee on Public Health was approved.

The following officers were elected for the ensuing year: president, Dr. Arthur W. Allen, president-elect, Dr. Leland S. McKittick, vice-president, Dr. Albert A. Hornor, secretary, Dr. H. Quimby Gallupe, treasurer, Dr. Elton Hubbard, Jr., assistant treasurer, Dr. Norman A. Welch, orator, Dr. John W. O'Meara. It is a pleasure to welcome Dr. Allen to his post and to rest secure in the knowledge of his ability to discharge its manifold functions.

The general sessions, constituting a well rounded program of clinical and scientific papers, were held in the Little Theater of the Worcester Memorial Auditorium beginning on the morning of May 24, and continuing through May 26.

The annual meeting of the Society took place also on the morning of May 24 and was highlighted by the President's report on the state of the Society, the awarding of prizes to three medical students and the annual oration.

As previously instructed by the Council, the Committee on Medical Education, on nomination by the deans of the three medical schools in the Commonwealth, had selected a fourth-year student from each school "who best exemplifies those intangible qualities which serve to designate him as the good physician." These students were Sylvan B. Baer, of Boston University School of Medicine, Henry S. Harvey, of the Harvard Medical School, and William H. Ellswood, of Tufts College Medical School. They were presented with suitably bound and illuminated autographed volumes of the George R. Minot Symposium on Hematology. It is hoped that the presentation of these detours may become an annual event.

The oration of the year, appearing as the leading article in this issue of the *Journal*, was delivered by Dr. C. Sidney Burwell, dean of Harvard Medical School, on "Some Responsibilities of Medical Education."

Among the changes in the by-laws ratified at the annual meeting was a new section providing for the creation of an advisory board to the President, consisting of the five most recent past presidents of the Society.

The Woman's Auxiliary of the Society was simultaneously holding its first annual meeting at the Worcester Woman's Club. The following officers were elected for the coming year: president, Mrs. Charles E. Ayers, of Worcester, president-elect, Mrs. Howard F. Root, of Brookline, first vice-president, Mrs. George F. Wilkins, of Brookline, second vice-president, Mrs. Roy W. Layton, of Melrose, recording secretary, Mrs. Claude E. Welch, of Belmont, corresponding secretary, Mrs. John F. Conlin, of Boston, treasurer, Mrs. Edward L. Peirson, of Salem. Mrs. Leighton Johnson, the retiring president, is to be congratulated on the progress that the Auxiliary has made during her administration.

On the morning of May 25 the Shattuck Lecture, which has already appeared in the *Journal* of May 26, was delivered by Dr. Paul D. White of Boston on the subject "La médecine du coeur." In the evening, at the annual dinner, Roscoe Pound, LL.D., university professor emeritus of Harvard University and former dean of the Harvard Law School, de-

livered an address on "The Professions in the Society of Today."

A singularly happy event on this occasion was the presentation to Dr. James C. McCann of a memorial from the Society, in recognition of the great service that he has rendered to the practice of medicine as president of Massachusetts Medical Service.

In the planning of the program and the excellent arrangement of the exhibits, great credit is due to the state and local committees of arrangements.

THE DOCTOR AND THE MEDICAL LIBRARY

THE organization of the Associates of the Yale Medical Library, extending to physicians in Connecticut borrowing privileges formerly reserved to those connected with the School of Medicine, indicates a growing awareness of the value of the medical library in medical education. All doctors in Connecticut, as well as all Yale medical alumni, have been invited to become members of the group, whose purpose is to maintain and augment the present medical collections and to extend their usefulness to the medical community at large, for expansion of the facilities and services of the Library, the Associates are required to pay a small annual subscription fee and are urged to contribute books and other material. The response to this invitation has been encouraging. Both Yale University and the officers of the Associates deserve credit for making this excellent collection available to doctors in Connecticut.

A similar association of the Boston Medical Library and the Massachusetts Medical Society has enabled physicians in Massachusetts to share the benefits of an outstanding medical collection.¹ The annual report of the Librarian, printed elsewhere in this issue of the *Journal*, points out the increased use of the facilities of the Library in 1948, apparently owing to the extension of borrowing privileges to members of the Society. In return, the allocation of a part of the dues of Society members has provided vital financial support for the Library. This additional income, although welcome, is not sufficient to enable the Library to make the repairs and alterations in its plant that are essential to maximum efficiency: the Library still lacks the \$75,000 for the erection of new stacks.²

The doctors in Connecticut and Massachusetts may well be proud of their support of these institutions whose contribution to medical education is so great. It is to be hoped that the funds essential to continued and expanded usefulness will be provided by those who benefit most from the opportunities offered: the physician who is doing research on an important project for which the records of previous work are essential, the writer of medical articles who wishes to make an adequate survey of the literature on the subject concerned, and the doctor, specialist or general practitioner, who desires to keep abreast of medical progress in his own and related fields. A small contribution from each would guarantee continuation of privileges that might be considered a generous return on a wise investment.

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1. Editorial. Budget for 1949. *New Eng J Med* 239 155 1948
2. Editorial. *Ex libris*. *New Eng J Med* 240 271 1949

THERE LL ALWAYS BE AN ENGLAND

AN ANNOTATION, according to the latest ruling of Webster, is a note added by way of comment or explanation. The annotation, as featured in the *British Medical Journal* or *The Lancet*, is by way of being a minor editorial in that it sometimes reflects the editor's views. The full-dress editorial in the *British Medical Journal* or *The Lancet*, is a leading article. An annotation in certain American journals is classed as current comment. Other journals employ the same form without classification — a relatively safe maneuver.

A fascinating annotation, in *The Lancet* of January 15, 1949, considers the various aspects of the writing of a report, as discussed at a meeting of the section of epidemiology of the Royal Society of Medicine. Writing is defined by one authority participating in this discussion as a development of the art of speaking. On the type of speaker that the writer may be depends the style of his writing — if he is able to address large groups he may write for the general public, if he speaks best to an audience of one his reports should be written as though they were personal letters.

Professor A. Bradford Hill, the well known statistician, defends his own peculiar form of intellectual activity, cleaving to the table as opposed to the

graph. Conclusions, however, must be in accord with the figures. As a classic discrepancy a statute of George III is quoted "which required half the penalties paid under the Act to be given to the informer and half to the poor of the parish, but the only penalty it allowed was 14 years' transportation."

Dr. A. L. Banks, apparently a disciple of the Roman military writers, maintains that the important question to be decided is whether any report is necessary at all. If the decision is in the affirmative it should be sufficiently complete to kill the subject stone dead with one blow, and that is a lesson that some American authors who spin from a subject a dozen yarns for a dozen different journals should learn.

According to another disputant, three types of reports may be considered for three classes of readers. 'A report to a health committee should contain the facts and all the facts, a report to a senior officer should contain selected facts, and a verbal report to students should contain one fact repeated three times.'

BOSTON MEDICAL LIBRARY

INCUNABULA AND EARLY MANUSCRIPTS

During 1948 eighteen incunabula were added to the Bullard and other collections, making a total of 715 to January 1, 1949. The collection is now the largest in a medical library in the United States and is outstanding among the collections in the country. Notable additions include a unique copy of Baldovinus Sabaudiensis, *Ars memorativa* (c. 1485), Gentilis de Fulgineo, *Tractatus de balneis* (Sanctorso, 1473), *Somnia Danielis* (Rome, about 1482-1488), this edition not being recorded in the United States, Dominicus de Carpanis, *De nutrienda memoria*, (Naples, about 1476), Gaspar Torrella, *Dialogus de dolore cum tractu de ulceribus in pudendragra* (Rome, 1500), an early tract on syphilis, with which is bound three early sixteenth-century tracts of Torrella, Pythagoras, *Ludus* (Padua, about 1482), not recorded in the United States, and the second edition in quarto of Sprenger and Institoris, *Malleus maleficarum* (Speir, about 1491), a popular book on witchcraft issued a number of times in the fifteenth century of which the Library now has the second to fourth editions. Dr. William Norton Bullard, who gave the Library a substantial sum for the purchase of books and manuscripts issued before 1700, was greatly interested in this subject.

and presented to the Library a large collection of books on witchcraft and demonology, including a number of incunabula and early English imprints, to which there has been added the Deetjen library, with surprisingly little duplication

The Library is interested in acquiring a representative collection of medieval and early renaissance manuscripts relating to medicine and in all the learned languages of the period. During 1948, an Arabic manuscript of the fifteenth century on drugs, one in Hebrew of the fourteenth century on personal health and one in English of the fifteenth century, comprising the receipt book of an English physician, were added to this division, which now totals sixty-two items

COLLECTED WORKS

The Boston Medical Library has been interested for many years in the regularly published works of physicians and collections of reprints of individual authors and of institutions and has a very large division of this type of material, and is pleased to add to it as occasion offers

Collections of writings of one or more authors are important to libraries for reference purposes and fall into a number of classes, one of which is collections of reprints of single authors. These again may be divided into two classes, of general and special interest

Those on special subjects are in some cases very important. The Boston Medical Library has received recently the *Collected Reprints* of Dr. William G. Lennox, bound in five volumes and containing his published writings from 1919 to 1947, numbering 190 papers and monographs. Dr. Lennox is recognized as an international authority on epilepsy and allied conditions. Likewise, there are the current series of Dr. Samuel A. Levine, the noted heart specialist, 1915-1946, and that of Dr. Maxwell Finland, of the Boston City Hospital, on infectious diseases, chemotherapy and allied subjects, bound in three volumes, 1923-1945

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A notable general collection of reprints is that of Dr. William Osler, bound in seven volumes, 1870-1920, by Dr. Osler and distributed to libraries and friends by the doctor

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general class is well represented by the *Reprints of the Rockefeller Institute for Medical Research*, currently published, and now in its one hundred and thirty-fourth volume (1947). In the special division may be noted the *Collected reprints of the grantees of the National Foundation for infantile paralysis*, volumes one to eight (1928 to 1947)

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MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

GONORRHEA AND SYPHILIS — STANDARDS OF DIAGNOSIS, TREATMENT AND FOLLOW-UP STUDY

With the advice and assistance of the Advisory Committee to the Division of Venereal Diseases, the Massachusetts Department of Public Health has adopted standards for the diagnosis, treatment and follow-up study of patients with gonorrhea and syphilis who are seen in the state-co-operating venereal-disease clinics

On the basis of the changing terminology as applied to venereal diseases and particularly to syphilis, the following nomenclature has been adopted

I GONORRHEA

- 1 Acute — with or without complications
- 2 Chronic — involving the urethra (anterior and posterior), prostate, seminal vesicles, epididymis, vulva, cervix, pelvic contents, Bartholin's gland, joint, eye, meninges and other structures

II SYPHILIS

- 1 Primary — only if chancre is present.
- 2 Secondary — only if secondary manifestations are present and include recurrent secondary syphilis
- 3 Early latent — the presence of a symptomless infection characterized by a repeatedly positive standard blood test for syphilis with negative spinal-fluid serologic findings and with a history of a primary lesion within four years, or in the absence of history of initial lesion when the patient is less than thirty years of age.

4. Late latent — the presence of a symptomless infection characterized by a repeatedly positive standard blood test for syphilis with negative spinal-fluid serologic findings and with a history of a primary lesion for four years or more, or in the absence of history of initial lesion, when the patient is thirty years of age or more

5. Late syphilis

- A Mucocutaneous
- B Osseous
- C Visceral
- D Neurologic

(a) Asymptomatic

(1) Early — abnormality in the spinal fluid within four years after the primary infection in the absence of all symptoms and signs

(2) Late — abnormality in the spinal fluid four years or more after the primary infection in the absence of all symptoms and signs

- (b) Acute meningitis
- (c) Chronic meningovascular
- (d) Vascular
- (e) Tabes
- (f) Paresis
- (g) Taboparesis
- (h) Gumma
- (i) Primary optic atrophy
- (j) Other types

6. Congenital syphilis

A. Early — congenital syphilis in a child less than two years of age

B. Late — congenital syphilis in a child two years of age or more.

III CHANCROID

IV GRANULOMA INGUINALE

- 1 Exuberant
- 2 Ulcerative
- 3 Cicatricial
- 4 Other

V LYMPHOGRANULOMA VENEREUM

- 1 Anorectal
- 2 Genital
- 3 Inguinal
- 4 Urethral
- 5 Other

GONORRHEA

In general, a diagnosis of gonorrhea is made on history of exposure, clinical signs and symptoms, and positive smears and cultures

A complement-fixation test or skin tests for gonorrhea are not recommended

Smears

The laboratory diagnosis of acute gonorrhea in male patients may safely be made in the majority of cases on the basis of a positive smear, the method is less accurate in acute gonorrhea in the female. In chronic gonorrhea in both male and female, the smear method alone is unreliable, and the cultural method should be used in addition

Cultures

The cultural method of diagnosis should consist of growing of the gonococcus on a standard medium (Mueller's starch agar, Difco's proteose No. 3, chocolate agar, Peizer's medium, Thayer's medium and so forth), performance of oxidase test, and sugar fermentation reactions

The taking of cultural specimens requires the careful attention of the physician. The ideal

method is to obtain a specimen and streak it immediately on a solid medium. If this cannot be done, the inoculum should be dispersed in the transport medium and mailed to a central laboratory. The results with this latter method — other conditions being equal — varies directly with the interval between the taking of the specimen and its being placed on the cultural medium. If there is a delay of forty-eight hours before plating, indirect cultural methods are for all practical purposes worthless.

A smear should accompany every specimen that is to be cultured.

The Inoculum

In the male, the urethral discharge may be used as an inoculum. The prostatic and seminal vesicle strippings may also be used. However, urinary-sediment culture is the method of choice in the absence of urethral discharge in male patients. The first morning urine should be used.

In female patients, cervical cultures are preferred. A nonlubricated cervical speculum should be used for visualization of the cervix. The cervical mucus is removed with a dry applicator, and the cervix firmly squeezed with the blades of either a bivalve speculum or a pair of forceps. A sterile, dry applicator is then passed into the cervical canal, rubbed firmly against its walls and immediately streaked on the solid cultural medium or placed in the transport medium. Cultures should also be taken from the urethra after it has been stripped or from the orifices of Bartholin's gland if that structure is involved.

Follow-up Study

Each treated case of gonorrhea should be followed by smears and cultures until at least two smears and cultures taken at weekly intervals are negative. The patient should be asked to return on the third day after treatment, and smears and cultures should be taken at this time. Thereafter, they should be taken at weekly intervals. It is agreed that a standard serologic test for syphilis should be done when the patient initially reports to the clinic for diagnostic examination, one week after treatment, and thereafter at monthly intervals until four months have elapsed from the date of the last exposure, or until two consecutive blood tests taken at least a week apart are negative (whichever is later).

Contacts

If a history of a definite onset exists, the patient should be interviewed for all contacts within two weeks prior to the onset of symptoms and all contacts subsequent thereto.

If there is an indefinite history of onset or if symptoms are denied, the patient should be questioned for all contacts within the past month.

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during pregnancy for syphilis may still have a positive standard serologic test for syphilis at term, and the problem of deciding whether or not congenital syphilis has been contracted will have to be decided if the baby has a positive serologic test at birth. It is proposed therefore that when such a situation arises in which the mother and the newborn infant have positive blood tests quantitative serologic tests be done on both mother and child and titers established, a repeat blood test be done on the third day and thereafter at weekly intervals up to one month to determine the serologic pattern of the child (the mother should be tested at weekly intervals for one month), and, after the first month, the baby be tested at two-week intervals up to the end of the third month. The mother should be followed as any other treated case of syphilis.

If this is a reagin transfer, the blood test should revert to negativity, usually by the second month and definitely by the third month. If the baby's blood test is positive at the end of three months, a diagnosis of syphilis either congenital or acquired should be entertained.

If the baby's serologic pattern is one of decreasing titers proceeding to negativity and if the serologic titers have always been lower or at the most equal to the month's reagin titer, the child may be considered nonsyphilitic at the end of three months provided it has negative blood serologic tests.

However, if the baby's reagin titer is significantly higher than the mother's, even though the baby's blood may temporarily revert to negativity, the baby if infected will show at some time before the twelfth week and usually by the eighth week increasing blood titers. The rise in titers is frequently accompanied by the onset of symptoms.

Whenever a patient has been treated for acquired syphilis during pregnancy and on birth the infant shows no evidence of congenital syphilis and a negative blood serologic test, the follow-up study of the infant should continue at two-week intervals for the first month and thereafter at monthly intervals until a minimum of three months' observation has been completed. If the test is still negative at the end of the three months, it is recommended that the infant be examined on the sixth, ninth and twelfth months.

The presence or absence of congenital syphilis, therefore, in a patient who is seen by the physician regularly should normally be established by the end of the third month. However, unusual conditions may necessitate a longer period of study.

Blood from the umbilical cord should not be used as a diagnostic criteria for congenital syphilis.

Whole-body x-ray films of the newborn infant should be taken on or about the fifteenth day.

The treatment of primary, secondary, latent syphilis and syphilis in pregnancy is as follows:

DRUG	DOSAGE PER INJECTION	TOTAL INJECTIONS
Inpatient		
Aqueous penicillin G	80,000 units every three hours	60 (4,800,000 units)
Alternative Schedule)		
Aqueous penicillin G	80,000 units every three hours	60 (4,800,000 units)
Bismuth	0.2 gm. every other day intramuscularly	5 (1 gm.)
Alternative Schedule)		
Aqueous penicillin G	80,000 units every three hours	60 (4,800,000 units)
Bismuth	0.2 gm. every other day intramuscularly	5 (1 gm.)
Mapharsen	0.04 to 0.06 gm. intravenously weekly	10 (0.4 to 0.6 gm.)
Ambulatory or office		
Procaine penicillin G in oil with 2 per cent aluminum monostearate	600,000 units in a single injection daily	10 (6,000,000 units)
Alternative Schedule)		
Procaine penicillin G in oil with 2 per cent aluminum monostearate	600,000 units in a single injection daily	8 (4,800,000 units)
Bismuth	0.2 gm. every other day intramuscularly	5 (1 gm.)
Mapharsen	0.04 to 0.06 gm. intravenously weekly	10 (0.4 to 0.6 gm.)

As an alternative schedule, the standard Army treatment, twenty-six-week arsenobismuth series may be given:

WEEK OF TREATMENT	INJECTIONS OF ARSENOXIDE*	INJECTIONS OF BISMUTH†
1	2 weekly	1 weekly
2	2 weekly	1 weekly
3	2 weekly	1 weekly
4	2 weekly	1 weekly
5	2 weekly	1 weekly
6	2 weekly	
7	2 weekly	
8	2 weekly	
9	2 weekly	
10	2 weekly	
11		1 weekly
12		1 weekly
13	Omit arsenoxide	1 weekly
14		1 weekly
15		1 weekly
16		1 weekly
17	2 weekly	
18	2 weekly	
19	2 weekly	
20	2 weekly	
21	2 weekly	
22	2 weekly	1 weekly
23	2 weekly	1 weekly
24	2 weekly	1 weekly
25	2 weekly	1 weekly
26	2 weekly	1 weekly
Totals	40	16

*Each injection consists of 0.04 to 0.06 gm. intravenously of diarsenolochlorophenarsine hydrochloride or mapharsen may be used.
†Each injection consists of 0.2 gm. intramuscularly.

All contacts of gonorrhea should be reported directly to the Massachusetts Department of Public Health on the forms provided for this purpose

Treatment

Uncomplicated gonorrhea The treatment consists of 300,000 units of procaine penicillin in peanut oil with 2 per cent aluminum monostearate given intramuscularly in a single injection

Failure to respond When uncomplicated gonorrhea has been treated as above but the discharge has persisted for three days or more, or if the smear and culture is still positive for the gonococcus, the patient should be treated with 600,000 units of procaine penicillin in oil with 2 per cent aluminum monostearate in a single injection intramuscularly

Complicated gonorrhea The therapy should include 300,000 units of procaine penicillin in oil with 2 per cent aluminum monostearate daily for at least three days. The length of treatment will depend on the clinician's judgment

Patients sensitive to the oil Patients who may be sensitive to the oil may be treated with an aqueous solution of crystalline penicillin G as follows: 50,000 units of penicillin intramuscularly, 50,000 units at the end of the first hour, and 100,000 units at the end of the second hour¹

Alternative schedule An aqueous solution of 300,000 units of procaine penicillin may be given intramuscularly in a single injection

Patients sensitive to penicillin Patients sensitive to penicillin should be treated with sulfathiazole or streptomycin. Sulfathiazole should be given in 1-gm doses by mouth every four hours for four doses each day. Treatment should be continued for a period of five days

Streptomycin may be given in doses of 40,000 units every four hours for three doses or in a single injection of 300,000 units (that is, 0.3 gm) in saline solution intramuscularly

Patients who are strongly suspected of having been exposed also to syphilis should be treated for their gonorrhea with sulfathiazole and not with penicillin to prevent masking of a possible syphilitic infection

Mixed infections Patients with gonorrhea and chancroid or those with gonorrhea and granuloma inguinale may be treated for both infections with streptomycin

Vulvovaginitis This condition should be treated with the drugs enumerated above. Estrogens should not be used in the treatment of gonorrheal vulvovaginitis

SYPHILIS

The diagnosis of syphilis should be made as early as possible since a favorable outcome depends on how long the patient has had the disease before treatment

Diagnostic Methods

A darkfield examination should be performed routinely on all genital lesions, particularly of the ulcerative type, and all suspicious secondary eruptions, the examination may be immediate or delayed. The immediate darkfield examination is the method of choice and is the only type recommended for general use. The success or failure of any darkfield examination depends considerably on the material to be examined. Therefore, to obtain a specimen for this important test, the base of the chancre should be grasped firmly and the surface cleaned with a wet saline sponge. Under moderate pressure, clear serum should be allowed to ooze forth. It may be necessary to abrade the surface of the chancre with dry gauze. A small amount of bleeding may result, and the blood should be wiped off with a dry sponge until clear serum appears. While the serum is being examined, the patient should receive a standard blood test for syphilis

No genital lesion should be treated locally or otherwise until repeated darkfield examinations have been performed. Under no circumstances should an anti-septic be applied locally

Physiologic saline dressings alone should be used pending darkfield examinations

A single darkfield examination alone, if negative, is of no significance. It should be repeated again and again

Latent Syphilis

Every patient should be carefully questioned for any signs or symptoms of acquired or congenital syphilis. Any condition that may give a false-positive blood test must be ruled out. The diagnosis of latent syphilis should not be made until a lumbar puncture has been performed. Therefore, all patients presenting themselves to the clinic with a positive standard serologic test should have a repeat blood test followed by a lumbar puncture. Lumbar punctures may be done in the outpatient department. The spinal fluid should be examined for cell count, globulin estimation, total protein and complement-fixation tests

The Wassermann laboratory will perform, on request, on all positive spinal fluids quantitative serologic tests, globulin estimations and total protein determinations. Cell counts should be performed by the physician directly after the specimen has been taken. The normal cell count is 1 to 4 per cubic millimeter. The normal protein is 35 to 40 mg per 100 cc. It must be remembered that a negative spinal-fluid serologic test does not necessarily rule out neurosyphilis

Congenital Syphilis

The use of quantitative serologic tests attains its greatest value in assisting the physician in making a diagnosis of congenital syphilis. A mother treated

NAME	HOSPITAL
Dr Bernard Appel	Lynn Hospital, Lynn
Dr Harvey Bianco	112 Main Street, North Adams
Dr Leo Blacklow	Waltham Hospital, Waltham
Dr Sarah H Bowditch	Assistant director, Division of Venereal Diseases
Dr George Bourgeois	Boston Dispensary, Boston
Dr G F Clark	Lawrence Clinic, Lawrence
Dr Lionel Cole	House of Mercy Hospital, Pittsfield
Dr G Marshall Crawford	Mt Auburn Hospital, Cambridge
Dr C Robert Damiani	Worcester City Hospital, Worcester
Dr Benjamin Ferris	Children's Medical Center, Boston
Dr William L Fleming	Massachusetts Memorial Hospitals, Boston
Dr Chester M Frazier	Massachusetts General Hospital, Boston
Dr Joseph Goodman	Beth Israel Hospital, Boston
Dr J Hartwell Harrison	Peter Bent Brigham Hospital, Boston
Dr William Hill	Massachusetts General Hospital, Boston
Dr James Hitchcock	Burbank Hospital, Fitchburg
Dr Lewis Kane	Boston Dispensary, Boston
Dr Israel Kopp	Boston Psychopathic Hospital, Boston
Dr C Guy Lane	416 Marlborough Street, Boston
Dr Harold L Leland	Board of Health Clinic, Lowell
Dr F W Marlow, Jr	Peter Bent Brigham Hospital, Boston
Dr T Frank Marnell	312 Main Street, Great Barrington
Dr Everett A Merrill	Lynn Hospital, Lynn
Dr Edward L Merrill	Board of Health Clinic, Fall River
Dr Joseph Muller	Memorial Hospital, Worcester
Dr Paul Nathan	Holyoke Hospital, Holyoke
Dr William W Nelson	New Bedford Co-operating Clinic, New Bedford
Dr Augustus S Rose	Boston Psychopathic Hospital, Boston
Dr Hyman Saphirstein	Beth Israel Hospital, Boston
Dr Allen Sherman	Newton-Wellesley Hospital, Newton
Dr John D Shinberg	Board of Health Clinic, Haverhill
Dr Harry C Solomon	Boston Psychopathic Hospital, Boston
Dr Edward C Sullivan	Springfield Hospital, Springfield
Dr Francis M Thurmon	Boston Dispensary, Boston
Dr Fred Weiner	Brockton Hospital, Brockton
Dr L Woodruff	Massachusetts General Hospital, Boston

NICHOLAS J FIUMARA, M D, M P H
Director, Division of Venereal Diseases

REFERENCES

- 1 Status of penicillin in treatment of syphilis Syphilis Study Section National Institute of Health December 1 1947
- 2 New and Nonofficial Remedies. 2-3-dimercaptopropanol in oil (BAL in oil) J A M A 137 568 1948

MISCELLANY

NOTE

Dr Franz Goldmann, associate professor of medical care at the Harvard School of Public Health, has been granted leave of absence from June through November, 1949, to serve as consultant to the Public Health Branch of the Civil Administration Division, Office of Military Government for Germany, under a project jointly sponsored by the Rockefeller Foundation and the American authority

CORRESPONDENCE

BRITISH DOCTOR LOOKS AT MEDICINE

To the Editor The following excerpt from a letter written by a former exchange medical student from England should prove of interest to the readers of the *Journal*

I hope you will forgive me if I seem terribly political but I thought I would mention a few of my feelings about

the Health Scheme since I think you may be interested I think I can honestly say that this move in England has started people thinking in many other countries besides our own I take one of the American medical journals, and each week I read with interest the comments that appear in the editorials upon the topic of nationalized and socialized medicine Incidentally, one of the best analyses of the subject I have read recently was in the *New England Journal of Medicine* Anyone would be very hard put to disagree with the basic principles of the scheme — namely, to try to provide medical care of reasonable standard to all people and to see that no one should be denied medical care because of poverty But I think many people will disagree with the methods adopted to bring this about. Quite frankly, I feel that the British medical profession is to blame to a large degree There do not appear to be the leaders of the caliber that is needed, and all through the negotiations I feel that the vast majority of the profession has been betrayed by the leaders One saw this particularly in the hospitals The seniors of the rank of "specialist," pleaded with the profession to withstand the demands of the Government, and then they themselves were the first ones to seek favor with the ministers and to secure the best positions In many ways the change was inevitable The cost of upkeep of a modern hospital, for instance, is a very considerable sum, and the voluntary institutions were falling into more and more debt With the present setup the Government is the main force controlling the expenditure of the service, and hence with this there is a distinct tendency for the policies of medicine to be dictated from a series of White Hall desks Check has been kept of everything, and so the number of forms that have to be completed is something quite phenomenal, particularly by the poor general practitioner, who has now become a sorting clerk He can devote only about three minutes at the very most to each patient and so if he suspects that there is a serious illness present he has to refer the patient to the hospital and thus lose any real medical work or else he spends the three minutes with the patient completing forms to provide him with free spectacles or extra milk or even a free wig Many people think this is a grand thing and trail along to the doctor to get something for nothing, little realizing that they are actually paying quite a lot for these "free" services I am afraid that British medicine is going to slide a long way behind the standards of other countries, for there is just no stimulus at all to provide a good standard Perhaps if there should be attempts to socialize American medicine you will see that the initiative comes from the doctors and not from the administrators

I am afraid that this has been a rather jumbled account but perhaps you can make a little sense out of it.

JAMES P O'HARE, M D

Boston

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender Books that appear to be of particular interest will be reviewed as space permits Additional information in regard to all listed books will be gladly furnished on request

Fractures and Dislocations For Practitioners By Edwin O Geckeler, M D, fellow of the American College of Surgeons, the American Academy of Orthopaedic Surgeons and the American Association for the Surgery of Trauma and diplomate of the American Board of Orthopaedic Surgery Fourth edition 8°, cloth 371 pp, 344 illustrations Baltimore Williams and Wilkins Company, 1948 \$5 00

The first edition of this short textbook for students and general practitioners was published in 1937 Dr Geckeler has revised this fourth edition to bring it up to date since the third edition was issued in 1943 New methods of treatment have been included, and the experiences gained during the last war have been incorporated in the text A good index concludes the volume The illustrations and publishing are excellent The author recommends the methods that he considers the simplest and most reliable The book should prove useful to the persons for whom it was written

The treatment schedules for various forms of syphilis are as follows

DRUG	DOSAGE PER INJECTION	TOTAL INJECTIONS
Early congenital syphilis		
Aqueous penicillin G	100,000 units per pound of body weight divided into 60-100 doses every 3 hours	—
Late congenital syphilis		
Treatment is the same as in acquired syphilis		
Interstitial keratitis — penicillin as in early syphilis accompanied by fever, unless contraindicated		
Late mucocutaneous manifestations		
Treatment is the same as in early syphilis		
Other late manifestations except neurosyphilis		
Patient prepared with bismuth therapy, 0.2 gm weekly for ten doses, followed by penicillin		
Aqueous penicillin G	80,000 units every 3 hours q 3 ^o for 60 doses	
Procaine penicillin G in oil and so forth	600,000 units daily for 10 days	
Neurosyphilis — asymptomatic, acute meningitis, chronic meningovascular, gumma		
Aqueous penicillin G	50,000 units every 3 hours	120 (6,000,000 units)
<i>(Alternative Schedule)</i>		
Aqueous penicillin G	100,000 units every 6 hours	60 (6,000,000 units)
Tabes, paresis, taboparesis, primary optic atrophy, congenital neurosyphilis and syphilitic nerve deafness		
Aqueous penicillin G	50,000 units every 3 hours	120 minimum (6,000,000 units)
Clinical or serologic relapse, or both (other than neurorelapse)		
Double penicillin dosage		
Standard Army treatment		
Neurorelapse and failure to improve		
Penicillin treatment repeated, accompanied by fever therapy unless contraindicated		

Treatment of Arsenical Reactions

BAL (2,3-dimercaptopropanol) in oil,² containing 20 per cent benzyl benzoate, is indicated in the treatment of hemorrhagic encephalitis due to arsenotherapy, arsenical dermatitis, and possibly postarsenical jaundice, but not homologous serum jaundice following parenteral therapy. It is useful as an adjunct in the treatment of agranulocytosis due to arsenic, but other measures, principally massive doses of penicillin, must also be employed.

The toxicity of BAL appears to be less in patients suffering from arsenic poisoning, but doses of 300 mg (5 mg per kilogram of body weight) may produce nausea, vomiting and headache, a burning sensation of the lips, mouth, throat and eyes, generalized muscular aches, with burning and tingling of the extremities, and a sense of constriction in the chest. The symptoms usually subside in thirty to ninety minutes.

Dosage In the treatment of arsenic poisoning, 3 mg per kilogram of body weight should be given intramuscularly as follows every four hours for the first two days, four injections on the third day,

and injections twice daily thereafter for ten days, or until complete recovery. In milder cases the dose may be reduced to 2.5 mg per kilogram of body weight.

FOLLOW-UP STUDY OF TREATED SYPHILIS

All patients treated for syphilis should have a two-year follow-up study. All syphilis except late syphilis should be followed at monthly intervals for one year, and at quarterly intervals during the second year. Each patient should receive a lumbar puncture between the sixth and the twelfth month after treatment. Late syphilis, because of individual variations and individual problems, should be followed at the discretion of the physician — that is, in uncomplicated neurosyphilis a follow-up study at intervals of three to six months may be used.

CONTACTS

Patients with primary syphilis should be questioned for contacts within three months prior to the onset of symptoms and subsequent thereto.

Patients with secondary syphilis should be questioned for contacts within six months prior to the appearance of the secondary manifestations and subsequent thereto.

Patients with early latent syphilis should be questioned for contacts within a one-year period. All marital and familial contacts should be checked as indicated.

For patients with late syphilis, marital and familial contacts should be examined.

With congenital syphilis, the parents and available siblings should be examined.

The problem will arise of patients who while on ambulatory treatment miss one or more day's treatment with procaine penicillin. If such a patient should lapse for only twenty-four hours, the rest of the procaine penicillin schedule should be continued. But if the patient should lapse for forty-eight hours or more, the procaine penicillin series should be begun over again.

SUMMARY

With the able assistance of the Advisory Committee to the Division of Venereal Diseases, the Massachusetts Department of Public Health has adopted standards for the diagnosis, treatment and follow-up study of patients with gonorrhea and syphilis for use in the co-operating venereal-disease clinics.

The members of this Advisory Committee are the present chiefs or the recently retired heads of the venereal-disease co-operating clinics. They therefore reflect the most authoritative opinion in the field of venereal diseases in Massachusetts.

The name of each committee member and the clinic he represents are as follows

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AURICULAR FIBRILLATION IN NORMAL HEARTS*

HUGH H. HANSON, M.D.,† AND DAVID I. RUTLEDGE, M.D.‡

BOSTON

AURICULAR fibrillation is not always associated with organic heart disease, and its presence may be the only sign attracting the examiner's attention to the heart. All cases of auricular fibrillation are fairly readily separated into two significant clinical groups — a minor group occurring in anatomically normal hearts and a major group occurring in damaged and diseased hearts. Emphasis should be placed on auricular fibrillation occurring in normal hearts because of its excellent prognosis, since this arrhythmia is most frequently observed in gravely damaged and decompensated hearts in which the prognosis is rather ominous.

Auricular fibrillation occurring in normal hearts has been variously termed "benign," "idiopathic," "auricular fibrillation of undetermined origin" and "auricular fibrillation in the absence of, or as the only manifestation of, cardiac disease." Although this array of terms may be somewhat confusing, they are all synonymous.

In 1911 Mackenzie¹ reported cases of auricular fibrillation in which no evidence of cardiac disease could be detected, and in 1913 Gossage and Hicks² demonstrated conclusively that such a condition existed.

MATERIAL

The material for this report consists of a review and follow-up study of all the cases of auricular fibrillation occurring in normal hearts that were seen at the clinic during the past two decades. The basis of selection was as follows: the presence of auricular fibrillation was confirmed by at least one electrocardiogram, taken at the clinic or elsewhere. If the patient had experienced two or more attacks lasting less than seven days and characterized by a sudden onset and termination, the fibrillation was considered paroxysmal, and if the condition existed longer than seven days it was considered established. After the presence of auricular fibrillation was confirmed, the following criteria were used to rule out cardiac disease: a history excluding rheumatic fever or allied disorders, hypertension, hyper-

thyroidism and coronary arteriosclerosis, a physical examination excluding cardiac enlargement, thrills, organic murmurs, hypertension and evidence of hyperthyroidism, a roentgenogram of the chest excluding abnormalities of cardiac size and configuration, an electrocardiogram excluding such abnormalities as marked axis deviation, significant T-wave changes and auriculoventricular or bundle-branch block, and laboratory studies excluding positive serologic tests, severe anemia, diabetes mellitus and an elevated basal metabolism.

A series of 651 cases of auricular fibrillation was reviewed, and only 30 cases (4.6 per cent) were found to have occurred in normal hearts. Of these, 10 (33.3 per cent) were established, and 20 (66.6 per cent) were paroxysmal (Table 1). Numerous cases of transient auricular fibrillation in apparently normal hearts were noted, but were not included in this report because the conditions under which they occurred inferentially excluded a normal myocardium. This point is elaborated below in the discussion of pathology.

INCIDENCE

That auricular fibrillation rarely occurs in congenital anomalies of the heart, syphilitic heart disease and bacterial endocarditis is well known. It may be present in any form of heart disease, but is most frequently observed in rheumatic (especially mitral stenosis) and hypertensive heart disease, hyperthyroidism and coronary arteriosclerosis; these four conditions account for approximately 89 per cent of all patients observed with this arrhythmia.³⁻⁵

Parkinson et al.⁶ found 85 per cent of their cases of paroxysmal auricular fibrillation associated with signs of cardiac disease. It is generally agreed by those familiar with the subject⁷⁻¹⁰ that approximately 6.5 per cent of all auricular fibrillation occurs in normal hearts, the arrhythmia being established in about a third of the cases and paroxysmal in the remainder. Auricular fibrillation is most frequently observed from the fourth through the sixth decade of life, reaching a peak incidence in the fifth decade, and it occurs most frequently in men. In the group reported here most of the established cases (70 per cent) were detected or occurred

*From the Department of Internal Medicine, Lahey Clinic.

†Fellow in Internal Medicine, Lahey Clinic.

‡Staff member, Department of Internal Medicine, Lahey Clinic.

Medical Research in France During the War (1939-1945) By Jean Hamburger, professeur agrégé à la Faculté de Médecine, Médecin des Hôpitaux de Paris, and Professeur Pasteur Vallery-Radot, member de l'Institut. 8°, paper, 306 pp., with illustrations Paris Éditions Médicales Flammarion, 1947

This work comprises a number of articles on a variety of medical subjects written by French physicians and translated into English for the English-speaking world. It embodies the results of medical research carried on by French physicians during the German occupation in World War II. The idea for the book came to Professor Vallery-Radot during a trip to the United States a few weeks after France was liberated, and he collaborated with Dr. Hamburger in assembling the collection of reports. The book is well published and should be in all medical libraries.

Venous Thrombosis and Pulmonary Embolism By Harold Neuhof, M.D., clinical professor of surgery, Columbia University College of Physicians and Surgeons, and consulting surgeon, Mount Sinai, Montefiore, Beth El and Hackensack, New Jersey, hospitals. 4°, cloth, 159 pp., New York Grune and Stratton, 1948. \$4.50.

This monograph is based on an intensive study of the subject for the purpose of working out a plan for the surgical management of pulmonary embolism. The text is divided into two parts: a discussion of the subject in its varying aspects, including the anticoagulant therapy with dicumarol and heparin, and a consideration of massive pulmonary embolism, based in part on a study of 88 fatal cases, and of etiology, diagnosis, prophylaxis and therapy (including embolectomy), and the mechanism of death. The author is convinced that the best results in these cases can be obtained by a special hospital team selected for the purpose. A bibliography and an index conclude the text. The monograph is well published and is recommended for all medical libraries and should prove valuable to physicians and surgeons interested in the subject.

Fielding H. Garrison: A biography By Solomon R. Kagan, M.D. 8°, cloth, 104 pp., with 8 illustrations. Boston Medico-Historical Press, 1948. \$4.00.

This volume constitutes a supplement to the *Life and Letters of Fielding H. Garrison*, published by Dr. Kagan in 1938. It presents additional biographic material on the early life of Dr. Garrison and his family and his service with the Army Medical Library, in the Philippines and at Welch Medical Library in Baltimore. The text is embellished with a large number of letters. An adequate index concludes the volume. The book is well published and should be in all medical-history collections.

Essentials of Pathology By Lawrence W. Smith, M.D., and Edwin S. Gault, M.D., associate professor of pathology and bacteriology, Temple University School of Medicine. With a foreword by the late James Ewing, M.D., Memorial Hospital, New York City. Third edition. 4°, cloth, 764 pp., with 740 illustrations. Philadelphia: Blakiston Company, 1948. \$12.00.

The first edition of this book was published in 1938. In this edition it has been revised and augmented with new material, and the text has been completely reset. Changes have been made in all the chapters, and some have been entirely rewritten. A large number of illustrative case histories have been inserted throughout the text. Likewise, the illustrations have been checked, some changes made, and sixty-one new figures added. A bibliography, arranged by chapters, and a good index conclude the volume. The type, printing and plate work are excellent. The book has been written primarily for students.

Dr. Robert A. Bolduc announces the opening of his office for the practice of general surgery at 180 Lincoln Street, Worcester.

MASSACHUSETTS PUBLIC HEALTH CONFERENCE AND NEW ENGLAND HEALTH INSTITUTE

The third annual meeting of the Massachusetts Public Health Conference and the New England Health Institute will be held at the University of Massachusetts, Amherst, from June 15-17.

INTERN PSYCHIATRIC AND SURGICAL RESIDENCIES

The United States Civil Service Commission has announced a medical-officer examination for rotating intern psychiatric resident and surgical resident positions in St. Elizabeths Hospital, Washington, D.C. The salaries for rotating interns are \$2200 for the first year and \$2400 for the second year, the salaries for psychiatric resident range from \$2400 to \$4100 a year, and those for surgical resident, from \$3400 to \$4150.

To qualify, applicants for the rotating intern positions must be third-year or fourth-year students in an approved medical school. Applicants for psychiatric resident and surgical resident positions must be graduates of a medical school with the degree of doctor of medicine, and must have completed a full year in an approved rotating internship. In addition to these requirements, applicants for appointment as surgical resident must have completed three full years as residents-in-training in surgery in an approved residency. No written test is required for this examination. The maximum age limit of thirty-five years is waived for persons entitled to veteran preference.

Further information and application forms may be obtained at most first-class and second-class post offices, from civil service regional offices or from the U.S. Civil Service Commission, Washington 25, D.C. Applications will be accepted by the Commission's Washington office until further notice.

CIVILIAN DOCTORS FOR PANAMA CANAL ZONE

Permanent appointments for physicians in the Civil Service now exist in the Panama Canal Medical Service. Owing to the high appeal of the health and living conditions in this tropical country, the number of appointments to be made is limited, and early applications are suggested, by the Panama Canal Office, from physicians who desire the opportunity for training and experience in tropical medicine under standard American living conditions.

Starting professional salaries are \$5599 and \$6540 a year, with free transportation to the Canal Zone provided for physicians, their families and household goods. In addition, doctors who receive appointments get two months paid vacation (including time lost by illness) and reduced fares on Panama Line passenger vessels.

Requirements for professional medical positions starting at \$5599 are graduation from an approved medical school, license to practice medicine in a state, ability to pass a standard physical examination, and completion of one year's internship in a hospital approved by the American Medical Association.

Requirements for professional medical positions starting at \$6540 are the same except that a minimum of three years of post-internship experience is required.

The Panama Canal Health Department operates several hospitals and a number of well equipped dispensaries offering excellent professional opportunities. The Health Department also maintains constant vigilance over the health conditions of the Canal Zone and the adjacent cities of Colon and Panama City.

Interested physicians should address their applications to the Chief of Office, The Panama Canal, Washington 25, D.C., or to the United States Civil Service Commission, Washington 25, D.C.

(Notices concluded on page xiii)

NOTICES

ANNOUNCEMENTS

Dr. Hyman Alford announces the opening of his office for the practice of pediatrics at 1775 Beacon Street, Brookline.

unrestricted existence well into their fifth decade of life without evidence of heart disease. Case 9 is of exceptional interest, the patient maintains that his pulse has always been irregular, and that all the males in his family have a similar pulse

he had auricular fibrillation. He is now seventy-nine years old and has experienced forty-four years of confirmed auricular fibrillation without symptoms, cardiac limitation or the use of drugs. His father and brother both of whom had had auricular fibril-

TABLE I (Continued)

CASE No	EFFECT	SUBSEQUENT	AGE	COMMENT
1	None	Excellent health (pulse)		Patient asymptomatic in 1947 auricular fibrillation present
2	Established auricular fibrillation	Patient remained normal	Age 80	No evidence of heart disease in 1942
3	Established auricular fibrillation	Patient asymptomatic	Heart disease	Pulse 70-80 no dizziness
4	Decrease in rate	Patient asymptomatic	Heart disease	In 1943 blood pressure 100/70 electrocardiogram showed auricular fibrillation x-ray film normal
5	Decrease in rate	Mild congestive heart failure excellent response to treatment	Age after 21 yr	Evidence of coronary sclerosis in 1948 blood pressure 140/70
6		Patient asymptomatic for 44 yr and then developed mild congestive heart failure with good response to treatment	44 yr and then	In 1948 hypertensive heart disease (blood pressure 140/80) evidence of coronary sclerosis
7*		In 1947 latent congestive heart failure developed	Heart failure	In 1948 coronary sclerosis patient asymptomatic
8	Excessive slowing of rate drug discontinued	Heart normal pulse 70 no dizziness		In 1948 heart normal patient asymptomatic
9		Patient asymptomatic for 44 yr in 1948 congestive heart failure developed evidence of coronary sclerosis		All males in paternal family have irregular pulse
10*		Pulse 80-90 no dizziness blood pressure 100/70		Heart normal
11	Cessation of attacks	Normal heart		In 1943 attacks less frequent
12	No effect conversion	No further attacks		Paroxysmal auricular fibrillation for 10 yr conversion to sinus rhythm heart normal
13	Decrease in attacks	Heart normal after 20 yr of fibrillation		
14		Patient died of stroke in 1946		Congestive heart failure never developed
15		Coronary occlusion in 1941 after 28 yr of fibrillation		In 1948 no angina patient working hard and in excellent health fibrillation still present
16		No follow-up heart normal		Patient Canadian doctor
17	None conversion	Last follow-up 2 yr after conversion no more fibrillation		Complete cessation of attacks
18	Attacks abolished	Last follow-up 1948 no dizziness no attacks heart normal		
19	No effect	Patient last seen 2 yr after evaluation heart normal fibrillation still present		
20	Attacks stopped	In 1944 carcinoma of rectum developed Miles resection performed		In 1945 no evidence of heart disease fibrillation still present
21	Attacks stopped	In 1945 blood pressure 160/100 heart normal		In 1944 fibrillation still present heart still normal
22		Attacks short and infrequent no symptoms		In 1947 heart normal fibrillation still present
23		Patient not interested in heart		No follow-up study
24	0.2 gm. daily prevents attacks	Patient has taken quinidine for 13 yr attacks occur if drug discontinued		In 1946 heart normal patient taking quinidine (brother with paroxysmal auricular fibrillation and normal heart)
25		In 1945 no more attacks		
26	Attacks ceased	1 yr after cessation of drug no attacks heart normal		
27		Fibrillation continued		Heart normal at 80 yr no problem
28	Attacks decreased	No treatment now attacks spontaneously less frequent		In 1948 heart normal 1 attack every 6 mo
29	Attacks abolished	No more attacks		
30	None Attacks abolished	Heart normal no more attacks		Fibrillation present 45 yr without symptoms

"This irregular pulse is a family legend passed on from father to son and is indicative of long life." The patient under discussion never visited a physician until thirty-four years of age, when he was told that

lution," had led a similar existence, dying at eighty-two and seventy-eight years of age, respectively, from "hardening of the arteries." This legend is very interesting, even in the absence of confirmation

in the fourth decade of life, and the paroxysmal (45 per cent) in the fifth. All the established cases and 55 per cent of the paroxysmal occurred in men.

Goldbloom and Segall¹¹ reported auricular fibrillation in an infant of 3 months whose heart was

Wolff¹² reported 5 cases of familial auricular fibrillation occurring in normal hearts, and stressed its benignancy so long as the ventricular rate remains slow and embolism does not occur. His patients were all athletic, enjoyed the "lesser evils" of life

TABLE 1 *Clinical Data in Cases of Auricular Fibrillation Occurring in Normal Hearts*

CASE No.	SEX	AGE WHEN CONDITION WAS DETECTED	DURATION	ASSOCIATED DISEASE	REASON FOR CLINIC VISIT	THERAPY
<i>Established auricular fibrillation</i>						
1	M	36	17	None	Evaluation	Quinidine
2	M	39	19 (paroxysmal auricular fibrillation) 6 (established auricular fibrillation)	Chronic anxiety	Irritable colon	Digitalis
3	M	35	0.8 (paroxysmal auricular fibrillation) 11 (established auricular fibrillation)	Anxiety	Evaluation	Digitalis
4	M	51	10	Anxiety	Evaluation	Digitalis
5	M	31	15 (paroxysmal auricular fibrillation) 6 (established auricular fibrillation)	None	Evaluation	Digitalis periodic
6	M	19	46	None	Evaluation	None
7*	M	38	26	None	Latent congestive heart failure	None
8	M	30	12	Peptic ulcer, inguinal hernia	Peptic ulcer	Digitalis
9	M	34	45	Arteriosclerosis	Mild congestive heart failure	None
10*	M	50	11	Carcinoma of stomach	Cancer	None
<i>Paroxysmal auricular fibrillation</i>						
11	F	26	22	None	Evaluation	Quinidine
12	M	43	10	Umbilical hernia	Evaluation	Quinidine, quinidine and digitalis
13	F	30	20	Irritable colon	Irritable colon	Digitalis
14	M	41	26	Cholecystitis with stones	Evaluation	None
15	M	35	35	Nasal polyps	Evaluation	None
16	M	45	8	Chronic sinusitis	Evaluation	None
17	F	42	10	None	Evaluation	Digitalis, Quinidine
18	M	48	12	Irritable colon	Irritable colon	Quinidine
19	F	51	2	Anxiety	Evaluation	Digitalis
20	F	42	22	Uterine polyps	Uterine polyps	Digitalis
21	M	53	27	Inguinal hernia	Hernia	Quinidine
22	F	38	7	Chronic nervous exhaustion	Evaluation	None
23	F	37	Years	Carcinoma of nose	Carcinoma	None
24	M	24	18	None	Evaluation	Quinidine
25	M	45	2	Anxiety (chronic)	Evaluation	None
26	F	21	3	Anxiety (chronic)	Evaluation	Quinidine
27	F	46	5	Menopause, arthritis	Evaluation	None
28	M	43	14	None	Evaluation	Digitalis, Quinidine
29	M	45	Unknown	Irritable colon	Irritable colon	Quinidine
30	M	32	5	None	Dyspnea	Digitalis, Quinidine

*Diagnosis made at insurance examination. Diagnosis made by local physician in all other cases except one which was discovered at clinic.

otherwise normal. Spontaneous conversion to sinus rhythm occurred at one year of age, and a ten-year follow-up study failed to reveal any evidence of cardiac disease.

and lived unrestricted without the necessity of drugs. In this series, Case 24 is an example of familial paroxysmal auricular fibrillation, and both the patient and his brother have enjoyed an active,

tions associated with attacks, but this is rare. Syncope has also been reported but is uncommon.

The one characteristic sign of auricular fibrillation in a normal heart is the slow ventricular rate with a negligible pulse deficit in the absence of digitalis therapy. In the established group of cases reported here, all had a ventricular rate between 60 and 90 per minute with an absent or negligible pulse deficit. The absence of a pulse deficit was commented upon by the examining physician in 50 per cent of the cases. The patients with paroxysmal attacks, during attacks, had a ventricular rate between 70 and 110 per minute in 90 per cent of the cases. Since most of these ventricular rates were taken from electrocardiograms obtained during attacks, the difference between apical and radial rates is unknown.

COURSE AND COMPLICATIONS

Patients with established auricular fibrillation may remain asymptomatic indefinitely. In 2 of the cases reported here it persisted over forty-four years before cardiac symptoms developed. Once established, the arrhythmia tends to remain permanently. An occasional case, however, reverts to sinus rhythm, spontaneously or under the influence of quinidine, after years of uninterrupted fibrillation.

Patients with paroxysmal auricular fibrillation may continue to experience attacks along a fairly regular course, or the attacks may become less frequent and of shorter duration, or cease—spontaneously or under drug therapy. Attacks may assume a progressive nature, becoming more frequent and of longer duration, and the arrhythmia becomes established. In such a course, digitalis is almost sure to result in established auricular fibrillation with symptomatic relief. In the cases reported here, 1 became established spontaneously and 2 by digitalis therapy, 10 cases were favorably influenced by drug therapy, paroxysms became less frequent in occurrence and of shorter duration in 1 spontaneously, and 9 continued along their usual course. Only 10 per cent of the paroxysmal cases usually become established.⁶

The duration and frequency of paroxysms are totally unpredictable. Brill^{21, 22} found that 90 per cent lasted less than seven days. In the cases reported here 90 per cent of the paroxysms lasted less than twenty-four hours, and 60 per cent less than four hours.

Complications from auricular fibrillation per se are rare, however, if the ventricular rate becomes rapid with a marked pulse deficit, anginal or syncope attacks may occur, and if this persists, congestive heart failure may supervene. Why the ventricular rate becomes rapid is unknown, but the resultant cardiac inefficiency proceeds to latent or manifest failure. This is a completely reversible type of heart failure and after decompensation

responds to the accepted forms of therapy, subsequent quinidization may effect conversion to sinus rhythm, resulting in a completely normal heart and preventing recurrence.^{6, 21, 22}

In addition to the previously mentioned complications that are peculiar to this condition, the patients, if they survive long enough, are subject to the malignant lesions, degenerative diseases and overwhelming infections of senility. Like all persons with normal hearts, many of them develop manifestations of coronary arteriosclerosis, coronary occlusion and hypertensive heart disease in later life. However, some die after years of auricular fibrillation, without clinical or pathological evidence of myocardial disease.

In this group of 30 patients, 20 have been adequately followed, and 65 per cent of these still show no evidence of heart disease. In those of advanced years, evidence of coronary arteriosclerosis has developed in 4 patients, 1 of whom has experienced an infarct, hypertensive and coronary arteriosclerotic heart disease has developed in 1, and hypertension in 2—1 died from a stroke. In 4 of these 7 patients some degree of congestive heart failure has occurred. The average age when failure made its appearance was sixty-four and a half years, and the average duration of confirmed fibrillation prior to failure was thirty-four years. It is interesting that in only 7 of these 20 patients has evidence of heart disease developed, and in these, manifestations occurred only after years of asymptomatic fibrillation and after they were approaching senility. Three patients have carcinoma, in these cases the heart remains normal.

DIAGNOSIS

There is usually little difficulty in determining the presence of auricular fibrillation on routine physical examination, but in all cases it should be confirmed by an electrocardiogram. Organic heart disease must be ruled out by the history, physical examination, roentgenogram, urine and blood studies and electrocardiogram. The criteria used in this study should be complied with before the diagnosis of auricular fibrillation in a normal heart is established.

Auricular tachycardia, auricular flutter and frequent extrasystoles may cause confusion on physical examination, but fortunately the electrocardiogram makes up for clinical inadequacies by vividly portraying the varying intervals between R waves and the absence of P waves.

In making this diagnosis one must beware of the young obese male, the diabetic patient and all persons in the sixth decade of life, for coronary arteriosclerotic heart disease may be concealed in these cases. Auricular fibrillation is frequently a manifestation of hyperthyroidism, and the nervous patient with a palpable thyroid gland cannot be dismissed without a thorough investigation. Rheu-

PATHOLOGY

That auricular fibrillation occurs in normal hearts has been proved repeatedly at post-mortem examination.^{8 10 11} Auricular fibrillation is a disturbance of auricular impulse formation and conduction that is a physiologic phenomenon and not a pathologic one. This was admirably demonstrated by Yater¹³ and summarized in his conclusion: "There is no pathologic change in the heart characteristic of auricular fibrillation." The pathology is mentioned here only to emphasize its absence.

The previously mentioned transient type of auricular fibrillation occurring in severe infections (typhoid, diphtheria, pneumonia, pleural effusions and fevers) following prolonged hypoxic surgical procedures (on the brain, chest and abdomen) and in various toxic states (diabetic coma, drug intoxication, inhalation of noxious gases and deep anesthesia) was purposely excluded from this report because the etiologic agent is obvious and pathologists are all too familiar with the myocardial edema, degeneration and inflammation associated with such conditions.

ETIOLOGY

Since an anatomic lesion has been excluded as the basis of auricular fibrillation one must explore the realm of physiology for an explanation. Friedlander and Levine⁷ advocated the theory of a "trigger mechanism" in which hypothalamic impulses transmitted via the vagus nerve produce the arrhythmia. Once the reflex is in motion it tends to become fixed, resulting in established auricular fibrillation unless some interference interrupts the circus movement. Other investigators working on the etiology of auricular fibrillation have presented evidence incriminating reflex vagal activity,¹⁴ increased intra-auricular distention¹⁵ and a combination of vagal tone and an exciting agent such as acetyl-beta-methyl-choline.¹⁶ However, these theories were presented to explain auricular fibrillation occurring in the presence of cardiac disease and are hardly applicable to that under discussion. Auricular fibrillation is frequently produced in animals for purposes of study by intravenous mecholyl or electrical stimulation of the myocardium.

Attacks of paroxysmal auricular fibrillation may be precipitated by nervous factors, and usually a combination of several are present. The arrhythmia is frequently observed in emotionally labile persons, and in mental workers who are subjected to stress. Many of the patients reported here were emotionally unstable and suffered from anxiety, nervous indigestion, fatigue and nervous exhaustion. Undoubtedly, reflex autonomic activity plays a role, but its exact relation remains unknown. Attacks of paroxysmal auricular fibrillation were associated with a psychogenic or functional element in 70 per cent of the cases studied. 30 per cent of

patients experienced attacks precipitated by anxiety, 25 per cent by indigestion, and 10 per cent by exhaustion and fatigue, and 5 per cent blamed alcohol and tobacco. Paroxysms occurred in response to any one of several psychogenic stimuli in some patients, and in a few the stimuli seemed to be additive in effect. No precipitating factor or known etiologic influence could be elicited in the cases of established auricular fibrillation.

PHYSIOLOGY

Auricular fibrillation is manifest by a totally disorganized multitude of fibrillary twitchings in the auricular muscle that convert it into a quivering mass of myocardium. The circus theory of auricular fibrillation is most widely accepted at the present time. Smith, Walker and Alt¹⁷ adequately demonstrated that in auricular fibrillation with a pulse rate below 100 and a negligible pulse deficit the cardiac output is normal, and that it diminishes as the pulse deficit increases. They also found that conversion of controlled auricular fibrillation to sinus rhythm did not increase the cardiac output. These findings were true of normal hearts and damaged hearts, in the absence of valvular lesions. By direct intra-auricular measurements, Stewart, Crawford and Gilchrist¹⁸ showed that auricular fibrillation with a nearly regular rhythm did not diminish the rate of blood flow. Buchbinder and Sugarman¹⁹ demonstrated, by direct measurements, that the arterial blood pressure is constant in cases of auricular fibrillation with a nearly regular rhythm. Hence, in normal or controlled auricular fibrillation, the cardiac output and the rate of blood flow are not diminished and the blood pressure is constant, ensuring adequate tissue oxygenation and normal tissue metabolism. Since auricular fibrillation in normal hearts is characterized by its slow ventricular rate and negligible or absent pulse deficit, it appears to be an efficient physiologic mechanism.

SYMPTOMATOLOGY

The symptomatology of this arrhythmia varies from an unawareness of its presence to partial incapacitation in the anxious and introspective. The group of cases reviewed here revealed that 80 per cent of the patients with established auricular fibrillation were unaware of its presence and asymptomatic, whereas the 20 per cent who experienced preceding paroxysmal attacks noted only palpitation and this symptom disappeared with establishment. It is remarkable that none of these patients were "heart conscious." Although 95 per cent of the patients with paroxysmal attacks experienced palpitation, the remaining 5 per cent were unaware of its presence until enlightened by the family physician. Other complaints associated with paroxysms were faintness, giddiness, exhaustion, slight dyspnea and anxiety. Wolff²⁰ reported angina pec-

intake, morphine, oxygen and mercurial diuretics as indicated and digitalized to control the ventricular rate and decrease the pulse deficit. After compensation is regained the arrhythmia may be converted to sinus rhythm by quinidine therapy, with gratifying and lasting results. Quinidine should not be used before compensation is restored because conversion may result in an uncontrollable tachycardia or embolism. When the manifestations of a complicating cardiac disease appear, the treatment is that of the underlying disease.

The young patient with auricular fibrillation and a normal heart is the ideal subject for quinidine therapy, however, one must weigh the benefits to be gained against the potential danger to the patient. Here the only real risk of quinidine therapy is that of sudden death from respiratory paralysis, ventricular fibrillation or cardiac arrest, and this has an incidence of about 1.8 per cent.²⁶ Because of its inherent risks, therapy should never be advocated for the sake of treatment. Sokolow²⁷ has advocated the use of quinidine routinely in patients with early auricular fibrillation and a normal heart, to prevent subsequent embolism, however, it is doubtful if such prophylaxis is justified. If quinidine therapy is to be instituted, the patient should receive two test doses of 0.09 to 0.2 gm four hours apart, and if no untoward symptoms occur the dose should be increased by 0.2 gm every four hours until conversion is effected or mild toxic symptoms such as nausea, tinnitus and diarrhea develop. After conversion is effected the patient should be placed on a maintenance dose of 0.2 gm three or four times a day for a brief period, and this gradually worked down to a minimal maintenance dose, which is frequently as low as 0.09 gm three times a day. This maintenance dose may be continued indefinitely if toxic symptoms do not appear.

In the group of patients reported here 36.6 per cent received no treatment, quinidine converted 16.6 per cent and diminished attacks in 10 per cent, digitalis established the preceding paroxysmal fibrillation in 6.6 per cent and diminished attacks in 6.6 per cent, and combined digitalis and quinidine produced conversion in 3.5 per cent. Digitalis had no effect on 20 per cent of the cases, and quinidine on 25 per cent of the cases in which they were used. One patient in this group has been on a maintenance dose of quinidine for fifteen years, and attacks still occur when the drug is discontinued.

SUMMARY

Auricular fibrillation, established and paroxysmal, does occur in normal hearts and accounts for approximately 6.5 per cent of all cases of this arrhythmia observed. It occurs most frequently in men and may make its appearance at any age. The patient usually experiences no symptoms, or is aware only of palpitation. The only unusual cardiac finding is slow auricular fibrillation with an absent or

negligible pulse deficit. This type of auricular fibrillation is physiologically reasonably efficient, maintaining an adequate cardiac output, a normal rate of blood flow and a constant arterial pressure. The etiology is unknown, but increased autonomic tone appears to play a part. Complications are rare, and the arrhythmia may persist for years without evidence of cardiac disease. The prognosis is that of the underlying myocardium, and the arrhythmia itself appears to be without significance. Treatment is not indicated unless complications develop, and the therapy is that of the complication.

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matic heart disease may also be associated with auricular fibrillation of long standing, and one must make a careful search for valvular murmurs, remembering that the presystolic accentuation of mitral stenosis often disappears in the presence of auricular fibrillation. When murmurs are present they must be carefully evaluated. The roentgenographic shadow must be carefully scrutinized for a prominent conus, and a fluoroscopic examination of the chest made to rule out a distended left auricle. A history of previous hypertension must be sought, and the axis deviation of the electrocardiogram taken into consideration.

In the group reported here, 33 per cent of the cases were discovered at the clinic, 66 per cent were discovered at routine life-insurance examinations, and 90.1 per cent were diagnosed by the family physician. It is interesting that 60 per cent of these patients came to the clinic for an evaluation of their cardiac status subsequent to the discovery of the arrhythmia, and 40 per cent came for unrelated conditions.

PROGNOSIS

The ultimate prognosis of auricular fibrillation occurring in normal hearts is dependent upon the maintained integrity of the myocardium, and is independent of the arrhythmia. The myocardium is subject to all the stresses, inflammations and degenerative changes of life, and if these occur, the prognosis becomes that of the underlying disease. When the arrhythmia makes its appearance after the fifth decade, the patient must be followed closely for myocardial disease, which may become manifest at any subsequent time.

Clinicians are well aware of the tendency for thrombus formation and subsequent embolism in auricular fibrillation, however, their statistics are compiled from cases of organic heart disease in which the distended auricles, slowed circulation of congestive heart failure and mural thrombi of previous infarction furnish ideal conditions for such accidents. Since auricular fibrillation occurring in normal hearts eliminates the stagnant auricular circulation and mural thrombi necessary for embolism, it is doubtful if such an accident ever occurs in this condition prior to the appearance of a complicating myocardial disease.

Numerous cardiologists have commented upon the excellent prognosis²³ and benignancy of this condition and state that the incidence of cardiovascular complications, occurring only after years of fibrillation in elderly persons, and the mortality rate are that of the general population.^{10, 24} They also believe that the condition is much more common than is generally recognized.²³ The benignancy of auricular fibrillation alone is exemplified by the observation that in a follow-up study of ten years or more among thyrocardiac patients who had been operated on for hyperthyroidism, the survival rate in those with established auricular fibrillation was

no less than that in those with normal rhythm.²⁵ Master and Eichert²⁵ stressed the temporary incapacity resulting from this condition in military personnel, however, it is doubtful if this would occur in civilian life, except in a confirmed neurotic. The excellent prognosis of auricular fibrillation occurring in normal hearts is in marked contrast to that occurring in diseased hearts, in which the expectancy of life is two and a half to seven years.

None of the group of patients reported here ever suffered incapacity for work or recreation because of auricular fibrillation itself, and several underwent as many as three major surgical procedures without cardiovascular complications of any type.

THERAPY

All these patients should receive an adequate explanation of their condition and should be reassured that it is benign. If precipitating factors can be determined in the paroxysmal type, an attempt should be made to remove them, and the patient advised to get more rest, relaxation and diversion of interests—with or without the aid of mild sedatives.

In dealing with these patients it should be remembered that the health of the majority of them will not depend on any form of drug therapy.²⁴ In slow, established auricular fibrillation with a negligible pulse deficit the cardiac dynamics are physiologically normal, and nothing is to be gained by conversion to sinus rhythm. The usual case of paroxysmal auricular fibrillation with infrequent attacks of short duration is definitely not benefited by therapy. However, if attacks are progressive and associated with disabling symptoms, therapy is indicated. As a therapeutic guide, attention should be focused upon the ventricular rate, for when this becomes rapid with a marked pulse deficit, cardiac efficiency is diminished, compensation is threatened and therapy is indicated. A rapid ventricular rate, and not the presence of auricular fibrillation, is the indication for drug therapy.

Two drugs, quinidine and digitalis, are widely used in the treatment of auricular fibrillation. Quinidine is the drug of choice for converting fibrillation to sinus rhythm because of its depressive action on vagal tone, cardiac muscle and junctional tissue conduction, and it will effect conversion in 65 to 75 per cent of the cases in which it is used. Digitalis and its glycosides are largely reserved for slowing the ventricular rate in congestive failure by virtue of their ability to increase vagal tone, the refractory period of auricular muscle and the time for conduction in junctional tissue. Paroxysmal auricular fibrillation of a progressive or disabling nature may be readily controlled by quinidinization to maintain sinus integrity or digitalization to establish the arrhythmia. If congestive heart failure supervenes, the patient should be placed at bed rest, given an acid-ash, salt-free diet, a normal fluid

intake, morphine, oxygen and mercurial diuretics as indicated and digitalized to control the ventricular rate and decrease the pulse deficit. After compensation is regained the arrhythmia may be converted to sinus rhythm by quinidine therapy, with gratifying and lasting results. Quinidine should not be used before compensation is restored because conversion may result in an uncontrollable tachycardia or embolism. When the manifestations of a complicating cardiac disease appear, the treatment is that of the underlying disease.

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THE SCHICK STATUS OF 18,000 YOUNG ADULT MALES*

JANE WORCESTER, DR P H,† AND F S CHEEVER, M D ‡

BOSTON

THE incidence of diphtheria in the United States as a whole declined from 1924 to 1945. However, in 1945 there were 18,606 cases of the disease—a larger number than had been reported since 1939. The various sections of the country did not share alike in this increase. Table 1, which presents the cases during the period 1939–1947, shows that in New England, for example, the number of cases reported in 1946 was approximately three times that reported in 1943. In the Mountain

makes it of interest to present the results of a Schick survey among some 18,000 naval recruits carried out during the period October, 1941, to January, 1942, instigated by and performed under the direction of Captain LeRoy D Fothergill, MC, USNR. Since these men were drawn from all over the United States, it was believed that an analysis of their immunity status (as determined by the Schick test) by geographic area might throw some light on the causes of these phenomena. In the

TABLE 1 Cases of Diphtheria in the United States *

REGION	1939	1940	1941	1942	YEAR 1943	1944	1945	1946	1947	AVERAGE ANNUAL CASE RATE per 100 000
New England	399	266	291	293	250	327	390	737	602	5
Middle Atlantic	2 524	1 597	1 310	1 127	960	856	975	1 832	1 453	5
East North Central	3 880	2 321	2 290	1 921	1 834	1 588	2 132	2 416	1 419	8
West North Central	1 582	1 197	1 204	1 062	1 292	1 411	1 617	1 813	1 117	10
South Atlantic	7 032	3 703	5 866	5 148	4 082	2 546	4 433	2 970	2 727	24
East South Central	2 766	1 639	2 023	1 750	1 570	1 797	2 554	1 735	1 490	18
West South Central	3 324	2 759	3 160	3 134	2 471	3 115	3 705	2 424	1 816	22
Mountain	1 073	825	895	734	663	706	770	792	689	19
Pacific	1 473	1 229	948	1 091	1 686	1 805	2 030	1 704	1 092	15
Totals	24 053	15 536	17 987	16 260	14 808	14 151	18 606	16 423	12 405	13

*The regions are the ones used by the United States Public Health Service and the Bureau of the Census.

states, on the other hand, the reported cases varied relatively little. The average annual case rates, also shown in the table, varied considerably from region to region during this period. The rates tended to be low in the northern sections and high in the southern and western. The relative increase in morbidity has been greatest in the areas showing lower annual case rates.

This increase in the number of cases has caused a certain amount of alarm, although it has not been proved that it represents anything more than the usual cyclical behavior of the disease. Another disturbing event has been a change in the age distribution in certain areas, with a greater proportion of cases occurring in the older age groups.¹ In Massachusetts, for example, during the period 1942–1944, 43 per cent of the cases were in patients over ten years of age, whereas during the period 1932–1934 only 37 per cent of patients were over ten years of age. The aging of the population seems to have been insufficient to account for the shift in the age distribution of the cases.

The increased incidence of the disease in certain areas coupled with the shift in age distribution

preliminary report of this survey by Cheever,² exigencies of space made a discussion of these points impossible.

The recruits, the great majority of whom were white, received their Schick tests promptly after their induction into naval service. Consequently, the results of the tests reflect civilian rather than military experience with diphtheria. As previously described,² the Schick test was carried out by injection intradermally into one forearm of 0.1 cc of a standard diphtheria toxin so diluted that 0.1 cc contained 1/50 MLD. A Moloney test was performed at the same time by the injection of 0.1 cc of a 1:100 dilution of diphtheria toxoid into the other forearm by the intradermal route. The tests were read at the end of forty-eight hours and again at the end of one hundred and twenty hours. Data collected at the time of the test included name, age, place of birth, place of residence before and after the age of ten years, any history of an attack of diphtheria in the subject or in members of his immediate family and finally any history of active or passive immunization against diphtheria. Similar results were obtained when the material was tabulated according to place of birth, place of residence before age ten or place of residence after age ten. Therefore, only one of the residence classifications will be used here—namely, place of resi-

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dence before age ten Table 2 presents the percentages of Schick-positive reactors in the regions composed of the states in which the recruits resided before age ten The percentages of positive reactors are also shown for recruits residing continuously in urban or in rural areas and for recruits who migrated between urban and rural areas An area was called urban if it had 5000 or more inhabitants The migration history was based on the period from birth to age of induction and not on the period from birth to age ten The age distribution of the population should be kept in mind when the results are being discussed Forty-one per cent of the recruits were seventeen or eighteen years of age, and 44 per cent fell in the age

reactors in this group falls between those in the urban and those in the rural In the northern and western sections the recruits coming from rural areas show consistently higher percentages of positive reactions The average difference between the percentages of susceptibles in the rural and urban areas of these six sections is 12 In the three southern sections, on the other hand, where the percentage of positive reactors was found to be low, relatively larger numbers of susceptible persons were found in the urban areas The average difference between the percentages of positive reactors in rural and in urban areas is -7

Although it may be possible to explain the variation between the percentages of susceptible persons

TABLE 2 *Schick-Positive Reactors According to Residence*

REGION	TOTALS		URBAN		RURAL		MIGRATED	
	TOTAL TESTED	PERCENTAGE POSITIVE	TOTAL TESTED	PERCENTAGE POSITIVE	TOTAL TESTED	PERCENTAGE POSITIVE	TOTAL TESTED	PERCENTAGE POSITIVE
New England	1 529	42.9	1 194	41.3	160	56.2	175	41.7
Middle Atlantic	2 674	38.7	1 990	36.0	54	49.7	330	43.0
East North Central	2 923	46.9	1 725	46.5	645	55.8	557	40.0
West North Central	2 560	50.1	1 734	42.0	1 342	56.9	484	45.4
South Atlantic	3 110	15.1	1 095	19.7	1 578	11.8	637	14.1
East South Central	1 668	15.1	479	16.5	868	10.6	321	14.6
West South Central	1 685	15.5	561	19.8	662	13.1	462	13.6
Mountain	636	45.4	184	40.8	251	48.6	201	45.8
Pacific	1 596	45.5	784	40.3	556	52.2	456	42.5
Totals	18,381		8 744		6 014		5 623	
Averages		34.1		35.6		33.7		31.5

group nineteen to twenty-three Only 15 per cent were over twenty-four years of age

Inspection of Table 2 shows that the variation between the different sections of the country in the percentage of positive reactors is very large The South Atlantic and East and West South Central states have the lowest incidence of susceptible recruits—15, 13 and 16 per cent respectively The percentages of positive reactors in the other regions are considerably higher They vary from 39 per cent in the Middle Atlantic states to 50 per cent in the West North Central area The correlation between the percentages of the population susceptible to diphtheria in this young adult group and the morbidity rates for the total population during the period 1939-1947 (Table 1) is not close The New England and Middle Atlantic regions combine low morbidity with high susceptibility, whereas the South shows a low susceptibility combined with a high morbidity In the West, both the morbidity rates and the susceptibility seem to be high Presumably, these statements should not be interpreted in terms of the natural history of the disease without knowledge of the immunization programs in the various sections

The differences between the percentages of positive reactors in urban and in rural areas can be seen in Table 2 The migrating group has been omitted from discussion, since the percentage of positive

in the rural and urban areas of the different sections in terms of the presence of clinical disease, no entirely satisfactory explanation for the varying incidence of the disease itself is forthcoming Doull,³ writing in 1928, commented on the fact that diphtheria acts differently in the North and the South He found that deaths from diphtheria occurred at a relatively earlier age in the southern than in the northern states He also showed that in the 26 northern states with which he was working (1917-1924) deaths occurred at an earlier age in the more highly urbanized states The same statement could not be made of the southern states, which were on the whole rural but had a relatively high proportion of deaths from diphtheria in the younger age groups Doull concluded that infection was more widespread and consequently that frank cases of the disease not only were more common in the South than in the North but also showed a greater predilection for the younger age groups in the former area He made no comparison between diphtheria death rates in urban and rural areas of the same states Analysis of the death rates for the year 1922 shows that in the South the rural areas of the states had higher death rates than the urban, whereas in the North the reverse was true These death rates refer only to the white population Collins⁴ has demonstrated that during the years 1940-1941 diphtheria mortality rates were considerably higher

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other words, the percentage of immune persons increases with age. It is difficult to compare the trends on the basis of the graph. The amount of

owing to more frequent contact with the organism. It may be that in the age group under consideration there is little contact with the organisms in any

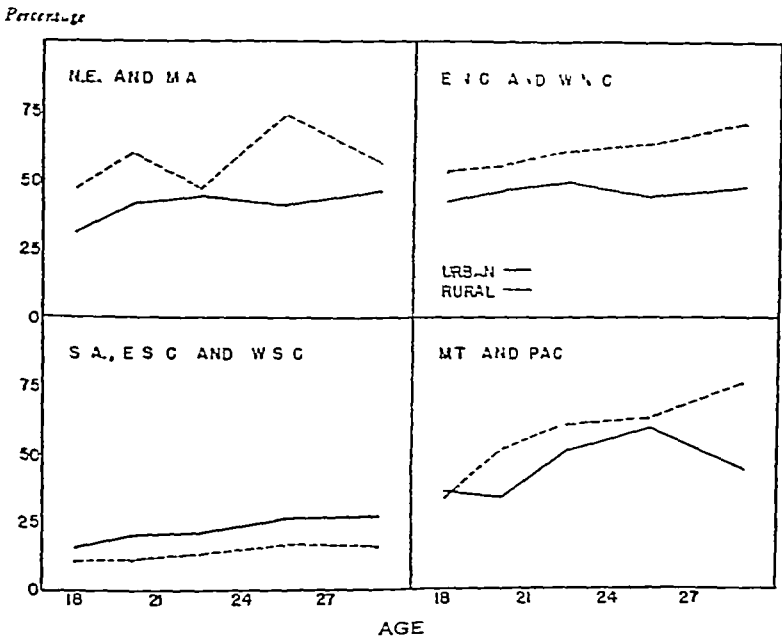


FIGURE 1 Schick-Positive Reactors According to Residence and Age

increase, calculated by the method of least squares without weights, in the percentage of positive reactors per year of age is given in Table 5. Beyond the fact that they are all positive, there seems to

of the regions. In any case, it is evident that neither contact nor immunization is sufficient to keep the percentage of susceptible persons from increasing after age seventeen.

TABLE 4 (Continued)

AGE	SOUTH ATLANTIC, EAST AND WEST SOUTH CENTRAL				MOUNTAIN AND PACIFIC			
	URBAN		RURAL		URBAN		RURAL	
	no. tested	percentage positive	no. tested	percentage positive	no. tested	percentage positive	no. tested	percentage positive
17-18	1,064	16.1	1,179	10.2	449	36.5	214	34.1
19-20	379	20.1	541	10.4	251	34.6	140	50.7
21-23	478	21.3	826	13.0	183	50.3	147	61.9
24-26	132	25.8	206	16.5	31	58.3	60	63.3
27-	82	26.8	126	15.9	34	44.4	46	76.1
Totals	2,135		2,903		968		607	
Averages		19.0		11.8		40.4		50.7

be little that can be said in general about these trends. The percentages of positive reactors are increasing more rapidly in rural areas where the percentages of positive reactors exceed those in the corresponding urban areas, although the trends in neither the urban nor the rural areas show any relation to the corresponding percentages of positive reactors. The trends are not sufficiently well determined to show that in regions where the percentages of immune persons are high the percentages themselves decline less rapidly with age, presumably

It was stated above that the immunization histories in this survey are believed to be unreliable. Table 6 gives the percentages of recruits who claimed to have been actively immunized against diphtheria in the urban and rural areas of the nine regions. The numbers upon which these figures are based were given in Table 2. The percentages appear to be very low. Also included in Table 6 is the average number of years since active immunization for recruits who claimed to have been immunized. Comparison of the percentages of

in the rural areas of the South than in the urban areas. However, in the remainder of the country the differences between the mortality rates in the urban and rural areas were small and inconsistent.

Material from which comparisons of morbidity rates in the urban and rural areas of the different regions may be made is hard to find. It is possible to compute from the Navy survey the percentages of recruits giving a history of clinical diphtheria

nizing infection than those living in the outlying districts. He found that the percentages of Schick-negative white children varied directly with the size of family and that families tended to be larger in the rural districts. However, the 1930 census of population, from which statistics on median family size are readily available, shows that rural families in all sections of the country tend to be larger than urban, although the differences are greatest in the South.

It appears that the percentages of immune persons (negative and false positive) found in the urban and rural areas in 1942 in this young adult group follow more or less closely the distribution of clinically recognized cases of the disease during the period when they were growing up. It must be remembered that, as yet, no mention has been made of the proportion immunized in the different regions, but unfortunately, as shown below, the immunization histories in this survey were not reliable.

Cheever,² in his preliminary report on this material, showed that in the entire group of recruits the percentage of positive reactors varied with age. It was 27 per cent at age seventeen and increased gradually to 45 per cent at age twenty-six. Apparently, a slow loss of immunity occurs with increasing age. There is some interest in ascertaining if this increase in the percentage of positive reactors proceeds in the same way in the urban and rural areas of the different regions. For this purpose, the nine regions of Table 2 have been combined into four, and for simplicity the migrating group has been omitted since the percentages of positively

TABLE 3 *History of Clinical Diphtheria According to Residence*

REGION	URBAN		RURAL	
	CASES	PERCENTAGE WITH CASE	CASES	PERCENTAGE WITH CASE
New England	36	3.0	4	2.5
Middle Atlantic	77	3.9	5	1.4
East North Central	72	4.2	18	2.8
West North Central	35	4.8	25	1.9
South Atlantic	50	4.6	40	2.9
East South Central	23	4.8	27	3.1
West South Central	37	6.6	21	3.2
Mountain	5	2.7	6	2.4
Pacific	43	5.5	9	2.5
Totals	378		155	
Averages		4.3		2.6

This percentage, which reflects approximately twenty years' experience with the disease, was found to be 3.7 for the entire group of recruits. Table 3 gives the number of cases and the percentages in the urban and rural areas of the different regions. Inspection of the table shows that the percentages are consistently greater in the urban than in the rural areas. It should be stated that the number of cases upon which the percentages are based is

TABLE 4 *Schick-Positive Reactors According to Residence and Age*

AGE	NEW ENGLAND AND MIDDLE ATLANTIC				EAST AND WEST NORTH CENTRAL			
	URBAN		RURAL		URBAN		RURAL	
	no tested	percentage positive	no tested	percentage positive	no tested	percentage positive	no tested	percentage positive
17-18	1,293	31.9	204	47.1	1,131	42.6	606	48.0
19-20	568	40.5	104	59.6	410	45.9	342	50.0
21-23	802	43.0	137	46.0	596	49.3	692	61.0
24-26	308	40.6	40	72.5	201	43.8	230	63.0
27+	213	45.1	29	55.2	119	47.9	115	70.4
Totals	3,184		514		2,457		1,985	
Averages		38.0		51.8		45.1		52.9

small and that the observations are subject to the limitations of memory.

Collins¹ gives diphtheria morbidity rates for the year 1935-1936 among residents of large and small cities surveyed by geographic section. He has shown that in these surveyed areas the diphtheria case rates were rather consistently higher in the towns and small cities than in metropolitan places in both the North and the South.

Chason,⁵ in 1936, discussed diphtheria immunity in rural Alabama. He stated that children living in the centers of the towns were less liable to immu-

reacting recruits in this group generally fall between those in the urban and those in the rural group at each age. Table 4 gives the number of recruits tested and the percentage of positive reactors at each age in the urban and rural areas of the four large regions. The percentages of susceptible persons are also shown in Figure 1. The differences between the percentages in the urban and in the rural areas at each age conform in general with the totals given in Table 2. Inspection of Figure 1 shows that the percentage of positive reactors increases with age in the urban and rural areas in each region, or, in

that the morbidity rates refer to the total population, whereas the information on immunization and the Schick status is based on young adults. It has been the purpose here to present certain

theria morbidity. Although the incidence of clinically recognized diphtheria in the different areas of the country is not high, the low level of immunity as evidenced by the high percentage of

TABLE 7 *History of Immunization Against Diphtheria*

REGION	SUBJECTS IMMUNIZED BEFORE 17		CURRENT RATE OF IMMUNIZATION PER 100 IN GROUP 1 1938 OLD 1933 1936	PERCENTAGE OF URBAN 17-18 Y. OLDS IMMUNIZED*
	PERCENTAGE IN GROUP 13 19 YR. OLD	PERCENTAGE IN GROUP 10 14 YR. OLD		
North East { New England Middle Atlantic }	32.5	61.0	0.50	16.4 20.7
North Central { East North Central West North Central }	45.5	59.7	0.91	21.0 29.4
Intermediate { West North Central South Atlantic }	32.9	4.9	0.46	29.4 27.5
South { South Atlantic West South Central }	20.5	1.9	0.75	27.3 37.1
West { Mountain Pacific }	40.8	5.1	1.49	31.0 16.0

*Navy survey (1942)

information regarding the Schick status of young adult males in different regions of the United States. On the basis of the Navy survey of 1942, this group of the population was found to be 13 to 16 per cent Schick positive in the South and 39 to 50 per cent Schick positive in the rest of the country. The percentage of positive reactors has increased with age in all parts of the country. Comment has been made upon the urban-rural distribution of the Schick-positive reactors. The young adult population of the rural areas of the North and West was found to be more susceptible than that of the urban areas, and in the South the reverse was true.

The available evidence suggests that whatever role active immunization may have played in reducing diphtheria morbidity it has had little demonstrable direct effect upon the immunity status of the general population as reflected by the results of this Schick survey. In both the North and the South the present Schick status appears to be directly related to the amount of clinical disease experienced in the last ten years. No such relation can be demonstrated in the Mountain and Pacific states, where the percentage of Schick-negative reactors is low in spite of a relatively high diph-

Schick-positive reactors among young men is not a cause for complacency.

This survey was carried out by the following officers under the direction of Captain L. D. Fothergill, MC, USNR: Captain R. W. Babione, MC, USN, Commander E. M. Bingham, MC, USNR, Commander F. A. Butler, MC, USN, Commander F. S. Cheever, MC, USNR, Commander J. N. DeLamater, MC, USN, Commander R. A. Mount, MC, USN, Commander O. F. Munch, MC, USNR, Lieutenant Commander L. R. Schoolman, MC, USNR, and Lieutenant A. B. Smith, HC, USN. Commander L. A. Barnes, MSC, USN, and Lieutenant (jg) Margaret Allen, WR, USNR, helped prepare the data for punch-card analysis.

The actual survey and the preliminary statistical analysis were carried out while Dr. Cheever was stationed at the Naval Medical School, National Naval Medical Center, Bethesda, Maryland, as a member of the Department of Epidemiology.

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recruits who were immunized with the average number of years since immunization shows that in areas where the percentages are high immunization seems to have been relatively more recent In the New England and Middle Atlantic regions, where the proportion of recruits who were actively immunized appears to be very low, the average number of years since immunization is large

zation in the 1935-1936 survey, shows the largest percentage in the Navy survey The North East, on the other hand, was found to be well immunized on the first survey and poorly immunized on the second Although there can be no doubt that the first survey, involving as it did careful questioning, is more accurate than the Navy survey, the reversal of the percentages is extraordinary It suggests

TABLE 5 Increase in the Percentage of Positive Reactors

REGION	URBAN		RURAL	
	TREND	PERCENTAGE POSITIVE	TREND	PERCENTAGE POSITIVE
New England and Middle Atlantic	0 9	38 0	1 0	51 8
East and West North Central	0 3	45 1	2 1	55 9
South Atlantic and East and West South Central	1 0	19 0	0 6	11 8
Mountain and Pacific	1 3	40 4	3 4	50 7

Memory seems to be playing an important part in these percentages
In a house-to-house canvass⁶ in 1935-36 of 200,000 families in 28 cities of 100,000 population or more, located in nineteen states, information was obtained about immunization against diphtheria, among other things Table 7 gives some of the history on immunization from this survey The first column of the table gives the regions into which the 28 cities were placed In braces are given the corresponding regions of the Navy survey, unfortunately, the correspondence is not exact The second and third columns give the respective percentages in the groups fifteen to nineteen and ten to fourteen years of age of people who had been immunized before 1935 The annual rate of immunization per

that during the period 1935-1941 considerably more active immunization was carried out among children and young adults in the southern and western states than in the northern ones It is unfortunate that the history of immunization from the 1942 survey is not sufficiently accurate so that it may be discussed in conjunction with the Schick-test material, which does not suffer from the same limitations
If the results of the 1935 survey are accepted as being more representative of the facts, collation of the information in Tables 1, 2 and 7 shows that no hard and fast statements can be made about the relations between the amount of immunization, the state of immunity as shown by the Schick test and the morbidity in the different sections of the country The northern region in general appears

TABLE 6 Percentages of Recruits Actively Immunized and the Average Number of Years since Immunization According to Residence

REGION	RECRUITS ACTIVELY IMMUNIZED		AVERAGE INTERVAL SINCE IMMUNIZATION	
	URBAN %	RURAL %	URBAN yr	RURAL yr
New England	13 9	14 4	9 11	9 91
Middle Atlantic	18 8	21 2	9 22	8 22
East North Central	20 1	26 7	8 56	7 11
West North Central	25 9	25 7	7 83	7 96
South Atlantic	25 3	35 2	6 98	6 49
East South Central	31 7	32 8	7 28	7 54
West South Central	28 7	31 6	6 59	7 43
Mountain	22 8	27 5	7 14	7 66
Pacific	16 5	23 6	8 26	7 51
Averages	21 0	29 1	8 08	7 47

100 for the year 1935-1936 among subjects fifteen to nineteen years of age is given in the fourth column The percentage of recruits seventeen to eighteen years old claiming to have been immunized in the urban population in the Navy survey of 1942 is shown in the last column It seems that the results could not be more in disagreement The South, which shows the smallest percentage of immuni-

to have been relatively well immunized, and yet shows a high percentage of Schick-positive reactors and a low morbidity rate The South, on the other hand, shows a low rate of active immunization, a high level of immunity and a high morbidity rate, and the far West has been relatively well immunized, and has a high percentage of positive reactors and a high morbidity rate It should be pointed out

that the morbidity rates refer to the total population, whereas the information on immunization and the Schick status is based on young adults.

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theria morbidity. Although the incidence of clinically recognized diphtheria in the different areas of the country is not high, the low level of immunity as evidenced by the high percentage of

TABLE 7 *History of Immunization Against Diphtheria*

REGION	SUBJECTS IMMUNIZED BEFORE 1955		CURRENT RATE OF IMMUNIZATION PER 100 IN GROUP 15-19 YR. OLD 1955-1956	PERCENTAGE OF URBAN 17-18 YR. OLDS IMMUNIZED*
	PERCENTAGE IN GROUP 15-19 YR. OLD	PERCENTAGE IN GROUP 10-14 YR. OLD		
North East { New England Middle Atlantic }	52.3	61.0	0.50	16.4 20.7
North Central { East North Central West North Central }	45.5	59.7	0.91	21.0 29.4
Intermediate { West North Central South Atlantic }	52.9	48.3	0.46	29.4 27.5
South { South Atlantic West South Central }	20.3	55.9	0.73	27.3 37.1
West { Mountain Pacific }	40.8	55.1	1.49	31.0 16.0

*Navy survey (1942)

information regarding the Schick status of young adult males in different regions of the United States. On the basis of the Navy survey of 1942, this group of the population was found to be 13 to 16 per cent Schick positive in the South and 39 to 50 per cent Schick positive in the rest of the country. The percentage of positive reactors has increased with age in all parts of the country. Comment has been made upon the urban-rural distribution of the Schick-positive reactors. The young adult population of the rural areas of the North and West was found to be more susceptible than that of the urban areas, and in the South the reverse was true.

The available evidence suggests that whatever role active immunization may have played in reducing diphtheria morbidity it has had little demonstrable direct effect upon the immunity status of the general population as reflected by the results of this Schick survey. In both the North and the South the present Schick status appears to be directly related to the amount of clinical disease experienced in the last ten years. No such relation can be demonstrated in the Mountain and Pacific states, where the percentage of Schick-negative reactors is low in spite of a relatively high diph-

Schick-positive reactors among young men is not a cause for complacency.

This survey was carried out by the following officers under the direction of Captain L. D. Fothergill, MC, USNR: Captain R. W. Babione, MC, USN, Commander E. M. Bingham, MC, USNR, Commander F. A. Butler, MC, USN, Commander F. S. Cheever, MC, USNR, Commander J. N. DeLamater, MC, USN, Commander R. A. Mount, MC, USN, Commander O. F. Munch, MC, USNR, Lieutenant Commander L. R. Schoolman, MC, USNR, and Lieutenant A. B. Smith, HC, USN. Commander L. A. Barnes, MSC, USN, and Lieutenant (jg) Margaret Allen, WR, USNR, helped prepare the data for punch-card analysis.

The actual survey and the preliminary statistical analysis were carried out while Dr. Cheever was stationed at the Naval Medical School, National Naval Medical Center, Bethesda, Maryland, as a member of the Department of Epidemiology.

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THE SEQUELAE OF EASTERN EQUINE ENCEPHALOMYELITIS

JOHN C AYRES, M D,* AND ROY F FEEMSTER, M D, DR P H†

BOSTON

WHEN cases of eastern equine encephalomyelitis occurred among human beings in Massachusetts in 1938, it was noted that profound damage to the central nervous system led to marked sequelae. To determine whether these changes are permanent and progressive or whether improvement can be expected, all the survivors who could be located were reinvestigated. The purpose of this paper is to report the present condition of these survivors.

Since several years have elapsed since the outbreak, a few facts regarding it are given for the information of those not familiar with the previous papers.

REVIEW OF OUTBREAK

Epidemiology

In July, 1938, equine encephalomyelitis was recognized in horses in southeastern Massachusetts, 269 deaths being reported in about ten weeks.

The disease first appeared in the upper basin of the Taunton River, which drains through nearby Rhode Island, and spread to contiguous areas, particularly northeast. Approximately 70 per cent of the deaths among horses occurred in a 30-mile square extending from the mouth of the Taunton River in the south to Boston on the north, and from the boundary of Rhode Island eastward to the coast of Massachusetts. Rhode Island to the west reported 55 cases among horses, and Connecticut, 29.

Inasmuch as the rainfall in southeastern Massachusetts and Rhode Island during the summer and early autumn was unusually heavy, mosquitoes were very prevalent in these areas. Furthermore, since the prevailing winds in this area are from the southwest, the tendency of the outbreak to spread in a northeasterly direction was attributed to the fact that infection-bearing mosquitoes were carried by these prevailing winds. The movement of infected horses and the flight of infected birds may have also played a role in the spread of the outbreak.

Almost simultaneously, a very fatal type of human encephalitis appeared in the same area, largely limited to children. The median date of reported deaths in horses occurred two weeks in advance of the median date of onset for cases in human beings. Although the prevalence of the disease was much greater among horses than among human beings, the rise and fall of the outbreak in these groups were similar. There was a slow increase for four weeks, rapidly reaching the peak

in two more, and then a much slower subsidence, the last case being reported sixteen weeks after the beginning of the outbreak.

The Massachusetts Department of Public Health investigated 44 cases of suspected equine encephalomyelitis.¹ From 9 of the patients, the eastern virus was isolated, and in 10 others, neutralizing antibodies for the same virus were found in the blood.^{2, 3} Eight more cases were diagnosed on the basis of the clinical picture and characteristic brain lesions at autopsy.^{4, 5} A diagnosis of equine encephalomyelitis was considered justified in 7 additional fatal cases because of characteristic clinical findings even though autopsies were not performed nor blood obtained for tests for neutralizing antibodies. Some patients had died before the etiologic agent had been suspected. Although 10 other cases were suspected, investigation revealed the diagnosis of equine encephalomyelitis to be unwarranted. About 70 per cent of the afflicted children were under ten years of age, the sex distribution being approximately equal. The mortality among the 34 patients was 74 per cent.

Clinical Picture

The clinical manifestations of the infection differed from other encephalitides in the greater severity of the symptoms and the high fatality. In infants the onset was sudden, but in older children and adults there were a few days of indisposition preceding active signs of encephalitis. The first complaints of older persons were commonly frontal headache and dizziness. The actual symptoms of encephalitis were almost invariably abrupt and characterized by fever, irritability, drowsiness, cyanosis and convulsions. The course of the disease was characterized by continued tremors or muscular twitchings, rigidity of the neck was constant, and a tense anterior fontanel was noted in infants, in whom a peculiar edema also developed about the eyes and in the upper extremities. A marked cyanosis was usually present, as was deep coma. The temperature was high, from 102 to 104°F, and when recovery occurred the temperature dropped by lysis over four or five days. Neutralizing antibodies appeared in the serum usually within six to eight days, and the blood showed a well marked response of neutrophilic cells. The cerebrospinal fluid was under increased pressure containing 200 to 2000 cells of which 60 to 90 per cent were neutrophils.

Surviving the acute stage, patients experienced coma and more or less rigidity of muscles for many days. Slow apparent return to normal was observed

*Epidemiologist, Division of Communicable Diseases, Massachusetts Department of Public Health.

†Director, Division of Communicable Diseases, Massachusetts Department of Public Health.

in a few cases, paralyzes, mental changes and other residual symptoms being more frequent. Death was commonly due to encephalitis but with some terminal evidence of myocardial insufficiency or pulmonary involvement.

Pathology

The pathological changes associated with the disease in man consisted of a profound, acute, disseminated and focal encephalomyelitis characterized by intense vascular engorgement, perivascular and parenchymatous cellular infiltration and extreme

or deterioration, with 2 requiring permanent hospitalization, 1 has chronic epilepsy with mental deficiency and hysterical behavior, in 1 neurologic symptoms, with some emotional instability, have developed, and 1 has made an apparently complete recovery so far as can be ascertained (Table 1). We have unfortunately been unable to trace 1 patient (T O'C). Three months after the acute episode, he showed no signs or symptoms of physical or mental impairment. Therefore, to our knowledge, 1 out of 34 patients has made an apparently complete recovery with no sequelae manifested

TABLE 1 Nine-Year Follow-up Study of Patients in 1938 Epidemic

PATIENT	AGE AT ONSET	SEX	RESIDUAL SYMPTOMS AT 1 YEAR	STATUS AT FOLLOW UP STUDY	
				NEUROLOGIC	MENTAL
D A.	12 mo	M	Mental retardation, right spastic hemiplegia.	Right hemiplegia with spasticity and pes equinovarus.	In 1945 chronologic age of 7 10/12 yr, mental age of 5 2/12 yr, I.Q. of 0.66; patient not going to school, socially obedient, suggestible.
R C.	12 mo	M	Mental deficiency, aphasia, left hemiplegia.	Left hemiplegia, aphasia, epilepsy (grand mal seizures 2 to 7 per mo).	Patient admitted to Monson State Hospital in July, 1942 (age 4); little or no mental development; patient deteriorated and helpless.
M. C.	18 mo	F	Mental deficiency, marked lack of emotional control, right hemiplegia, impaired vision, partial deafness; patient speaks only a few words.	Right hemiplegia, spastic generalized convulsions periodically.	Patient admitted to Wrentham State School in June, 1946 where chronologic age was 9 3/12 yr, mental age 1 yr, I.Q. 0.11; serious behavior problem, lack of emotional control.
D L.	4 mo	F	Mental retardation, strabismus, frequent convulsions.	Patient died in January 1940 at age of 2 1/2 yr during convulsive seizure; could not walk or sit, sixth-cranial-nerve palsy, 4 or 5 grand mal seizures per day.	Mental age of 2 mo with chronologic age of 15 mo.
R. R.	1 mo	F	'Decerebrate animal' and mass reflexes, eyes did not react to light.	Patient died in September 1944 at age of 2 1/2 yr during convulsive seizure; bilateral talipes equinovarus as many as 42 grand mal and 31 petit mal seizures per mo.	Extreme mental retardation; patient deteriorated and helpless.
L. F.	8 yr	M	Definite mental retardation (age about 3 yr) and partial aphasia.	Epileptic seizures began 1 year after acute episode and have continued since.	Mental retardation, cortical test March 1947, Hunt-Minn 64, memory quotient 66, vocabulary 4, spelling grade 3 to 4, hysterical behavior.
C D.	6 yr	M	Slight retardation in motor field, I.Q. 1.14.	'Slight Friedreich's foot on left.	Habit problem; patient 'very nervous'.
M. B.	6 yr	F	Patient dragged one leg for first year.	None.	None.
T O'C.	4 mo	M	None (at 3 mo).	Contact lost.	

degenerative changes in the nerve cells. The gross pathological manifestations were not specific.

FOLLOW-UP STUDY

Gettings,⁶ in 1941, reported his findings in following up all 9 surviving patients of the 1938 epidemic in whose blood neutralizing antibodies for the eastern variety of virus were found. In all cases except one, this follow-up study was made approximately one year after onset. All but 3 had disabling sequelae. Six showed evidence of cerebral degeneration, with mental retardation. Three patients continued to suffer from hemiparesis, 3 from complete or partial aphasia, and 1 from emotional instability.

In carrying out a nine-year follow-up study in these patients, we have found that 2 have died (deaths attributable directly to sequelae of encephalitis), 3 have hemiplegia and mental deficiency

up to this time, and another had no known defects early in convalescence when contact was lost. The mortality rate has been increased to approximately 90 per cent, with a complete recovery rate of only 3 per cent.

One can assume from this that any damage to the central nervous system during the acute phase is severe and permanent. As time goes on this damage does not improve but rather seemingly increases as more is demanded intellectually, emotionally and physically of the patients. It becomes evident that eastern equine encephalomyelitis not only is highly fatal but also carries a very poor mental and physical prognosis.

SUMMARY

The 1938 outbreak of eastern equine encephalomyelitis in southeastern Massachusetts is reviewed

Thirty-four persons were infected, 70 per cent being under ten years of age, 9 survived, and 6 had permanent sequelae after one year. One of the 9 survivors cannot be located, 2 of the 8 other survivors have died, 4 are hemiplegic, mentally deficient and emotionally unstable, 1 is mentally deficient, epileptic and hysterically inclined, 1 has a "slight Friedreich's foot" and is a habit problem, only 1 has made an apparently complete recovery.

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HEPATITIS, EXFOLIATIVE DERMATITIS AND ABNORMAL BONE MARROW OCCURRING DURING TRIDIONE THERAPY*

Report of a Case with Recovery

SAMUEL E. LEARD, M.D.,† WILLIAM E. R. GREER, M.D.,‡ AND I. CHARLES KAUFMAN, M.D.§

BOSTON

SINCE 1944, when Everett and Richards¹ described the anticonvulsive action of tridione (3, 5, 5-trimethylxazolidine-2, 4-dione), the drug has been used in human beings to control epileptic attacks, especially petit mal seizures. Varying toxic reactions have been described, but to our knowledge this is the first case in which hepatic dysfunction, severe exfoliative dermatitis and leukemoid bone-marrow changes have been reported in the same patient.

The first report on the clinical use of the drug made very little mention of toxic reactions or unpleasant side effects. In 1945 Lennox² noted that in the majority of adolescent or adult patients, but rarely in young children, there was an unusual sensitivity of the eyes to bright sunlight. In a later report on the use of the drug in 222 patients, varying toxic manifestations were noted³, 122 patients showed photophobia, 32 reported a rash, either

headache, 4 noted insomnia, poor appetite and nervousness, 3 had dizziness, pain in the eyes and nosebleeds, 2 complained of sleepiness, double vision and "poor circulation", and 1 had sneezing, hiccuping and aplastic anemia. Six per cent of 127 patients showed a decrease of polymorphonuclear leukocytes below 1600. Twenty-five per cent had an eosinophil count of 6 to 25 per cent, a complete hematologic report on these cases having been presented by Davis and Lennox⁴ in 1947. However, these side effects appeared to be of minor importance considering the beneficial effects in treatment of petit mal epilepsy, and the drug was sometimes rather loosely administered without due precaution. Butler⁵ and Perlstein and Andelman⁶ noted essentially the same relatively unimportant side reactions in later reports.

In May, 1948, Barnett, Simons and Wells⁷ described for the first time the nephrotic syndrome

TABLE 1 Studies of the Peripheral Blood

DATE	RED CELL COUNT	HEMOGLOBIN	HEMATOCRIT	RETICULO CYTES	ICTERIC INDEX	WHITE CELL COUNT	NEUTROPHILS	BAND FORMS	EOSINO PHILS
1948	$\times 10^6$	gm /100 cc	%	%	units	$\times 10^3$	%	%	%
May 13	—	—	43.5	—	15	10.5	21	13	18
May 17	—	12.6	39.0	—	10	10.2	33	9	28
May 21	—	13.3	38.0	—	—	12.2	41	20	5
July 10	—	12.3	40.0	—	6	12.0	65	6	1
July 28	4.42	12.4	40.0	0.9	7	10.8	55	—	2

acneiform or morbilliform, 18 described gastric distress or nausea, 9 had behavior difficulty, 7 had

occurring during tridione therapy. In their patient, a girl of sixteen years, edema, decreased serum al-

*From the Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals, and the Departments of Medicine, Psychiatry and Neurology, Boston University School of Medicine.

†Instructor in medicine, Boston University School of Medicine, chief resident in medicine, Massachusetts Memorial Hospitals.

‡Instructor in medicine, Boston University School of Medicine, resident in medicine, Massachusetts Memorial Hospitals.

§Associate in research and instructor in psychiatry and neurology, Boston University School of Medicine, chief of the Seizure Clinic, Outpatient Department, Massachusetts Memorial Hospitals, assistant visiting physician in neurology and psychiatry, Massachusetts Memorial Hospitals.

bumin and elevated cholesterol reappeared on two different occasions while she was taking tridione. With the withdrawal of the drug, the blood chemical findings and nephrotic signs disappeared after several months. White⁸ reported a somewhat similar case of nephrosis occurring in a seven-year-old boy who was treated with tridione.

Aplastic anemia and agranulocytosis have both been observed by several authors. Harrison et al⁹ reported a fatal case of aplastic anemia in 1946. Mackay and Gottstein¹⁰ described aplastic anemia and agranulocytosis from tridione. A case of fatal agranulocytosis in Great Britain¹¹ was reported in January, 1948. Carnicelli and Tedeschi,¹² in March, 1948, discussed a fatal case of acute pancytopenia following tridione treatment in a nineteen-year-old girl, including the post-mortem findings.

In the case reported below, toxic hepatitis, a leukemoid reaction in the sternal marrow and severe exfoliative dermatitis occurred in an elderly man after the use of tridione, with recovery of the patient. It is possible that the reactions were on the basis of an allergic reaction to the drug rather than a true direct organ toxicity. It is probable that if tridione had a direct hepatotoxic action this would have become evident in animal experiments, and cases of human toxic hepatitis would be much more frequent.¹³

CASE REPORT

A 69-year-old divorced, epileptic salesman was admitted to the hospital on May 9, 1948, with a chief complaint of generalized skin rash of 5 days' duration.

The family history revealed that his mother had had epileptic attacks starting at the age of forty years. In the past year he had had nocturia, which was diagnosed as being caused by hypertrophy of the prostate. During the past few years he had had slight shortness of breath and also occasional ankle edema. In the past year he had become forgetful and lacked power of concentration.

At the age of 8 years the onset of minor and major seizures had occurred. The attacks always began with an epigastric sensation, which traveled up to his head and sometimes ended there or went on to a major seizure with unconsciousness. Convulsions were never described, but he often noticed that his tongue had been bitten and also found evidence of involuntary urination and defecation on recovery. He had had only the epigastric aura (without unconsciousness) for

a generalized pruritic rash occurred and tridione was stopped. Two days later hiccuping, dark urine and anorexia began.

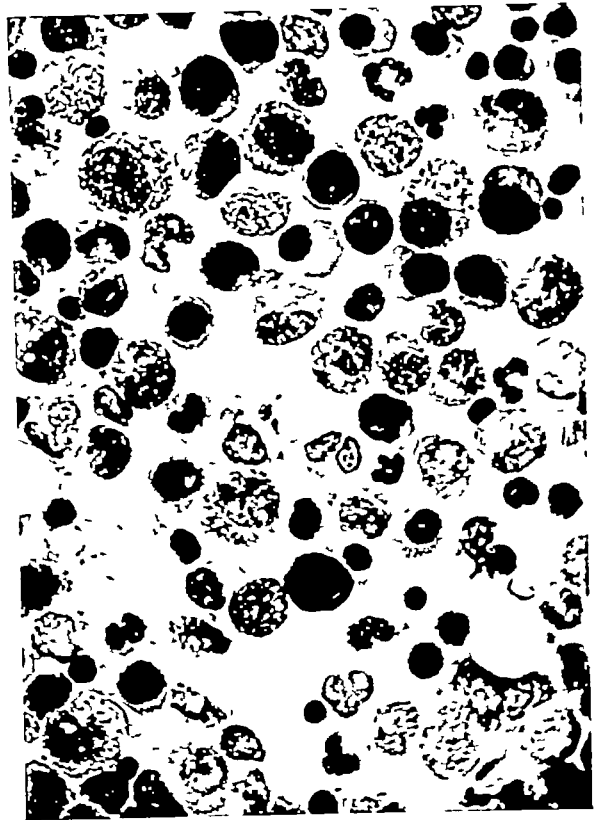


FIGURE 1 Aspiration Biopsy of the Sternal Marrow Performed on March 29 (Wright-Giemsa Stain x 800)

The marrow is markedly hypercellular, the hyperplasia including cells of both the erythrocytic and the myeloid series. There is a disproportionate increase in the more immature elements of the granulocyte series, myelocytes and metamyelocytes representing approximately 65 per cent of all leukocytes present. Plasmacytes and megakaryocytes are present in normal concentrations. Erythropoiesis appears to be active, and the progress of maturation normal in this series.

Physical examination revealed a generalized hemorrhagic, erythematous, blotchy, macular, confluent eruption involving the palms of the hands, soles of the feet, scalp, mucous mem-

TABLE 1 (Continued)

BASOPHILS	SMALL LYMPHOCYTES	LARGE LYMPHOCYTES	YOUNG MONOCYTES	ADULT MONOCYTES	MYELOCYTES	PRO-PLASMA-CYTES	PLASMA CELLS	PLASMA FORMS	PLATELETS
%	%	%	%	%	%	%	%	%	%
0.5	25	3.5	1	3.5	1.5	0.5	2.5	3.0	173,000
1.0	28	—	—	3.0	—	—	1.0	—	—
2.0	16	5.0	1	8.0	1.0	—	1.0	—	Normal
1.0	15	4.0	—	6.0	—	—	2.0	—	Increased
1.0	31	—	—	9.0	—	—	—	—	Normal

12 to 15 years prior to admission, having taken phenobarbital, 32 mg in the morning and 65 mg in the evening. Six or seven weeks before admission he had seen a new doctor, who told him to take tridione, three (0.3-gm.) capsules a day in place of phenobarbital. About 1 month before admission, he reduced the dosage to two capsules daily. Two weeks before admission, greenish-yellow vision, which was improved by green-tinted glasses, developed. Five days before admission

branes and lower extremities. There were numerous cervical and submaxillary small lymph nodes, and one 2-cm. node in the right axilla that was freely movable. The scleras were icteric. The pupils were not remarkable. The conjunctivas were injected. The retina showed no hemorrhages or exudates. The nasal mucosa was injected. The lips were slightly edematous and tender to palpation. The breath was fetid. A partial upper denture was present. The throat and mucous

membranes were injected. The tongue was dry and coated. No distention of the jugular veins was apparent. The chest was clear to percussion and auscultation. The left border of cardiac dullness was 8.5 cm from the midsternal line in the 5th interspace. There was normal sinus rhythm. The liver was palpable and slightly tender, and the edge was felt 7 cm below the right costal margin on inspiration. The spleen was palpable 3 cm below the left costal margin. Peristalsis was normal. A right reducible inguinal hernia was present. The prostate was moderately enlarged. Neuro-

presented evidence of markedly increased hyperplasia in the granulocytic series, and an abnormal degree of immaturity in that series, eosinophilia was likewise marked. The findings seemed consistent with those of myelogenous leukemia or severe leukemoid reaction, the latter indirectly being the correct interpretation in view of the findings obtained on the most recent examination, which must be regarded as within normal limits.

The nonprotein nitrogen was 23 to 40 mg per 100 cc. The total protein was 5.45 gm per 100 cc, with an albumin of 3.26 and a globulin of 2.19 gm. Prior to discharge the total protein was 7.02 gm per 100 cc, with an albumin of 3.26 gm. The serum bilirubin on admission was 3.2 mg per 100 cc direct, 4.3 mg total, and remained elevated for 3 weeks. At discharge it was 0.24 mg per 100 cc direct and 0.96 mg total. The alkaline phosphatase, which was 11.76 Bodansky units initially, rose to 14.13 Bodansky units and fell to 4.89 Bodansky units by the 3rd week. Thymol turbidity was 0. Cephalin flocculation was +++. The serum amylase was 16 units and later 8 units per 100 cc. Lumbar puncture showed an initial spinal-fluid pressure equivalent to 170 mm of water, the dynamics free, and the fluid clear and colorless, there were 43 red blood cells and 0 white blood cells per cubic mil-



FIGURE 2 Sternal Marrow on May 13 (x 400)

Cellularity of the marrow has decreased to a degree approaching normal, although the relative proportions of the more immature myeloid elements are essentially unchanged.



FIGURE 3 Sternal Marrow on July 28 (x 400)

The degree of proliferation and composition of the marrow is completely within normal limits, myelocytes and metamyelocytes now constituting approximately a third of the leukocytes present.

logic examination was negative except for absent patellar and Achilles-tendon reflexes bilaterally.

The temperature was 100.2°F (by rectum), the pulse 88, and the respiratory rate 18, the blood pressure was 125/75.

The urine showed a specific gravity of 1.006 to 1.022 and gave a +++ to ++++ test for bile. The urobilinogen was 1.16 on many occasions. Slight traces of albumin were noted in the sediment on several occasions. Bile was present for the first 6 days. Blood studies showed a sedimentation rate of 12 mm per hour on admission, which rose to 47 mm in the 3rd week and then fell to 30 mm prior to discharge. The hematocrit was 49 per cent on admission and 34 per cent on discharge. The blood Hinton reaction was negative. The hemoglobin was 15.5 gm on admission and 11.9 gm on discharge. The reticulocyte count was 0.7 per cent, and the platelet count 173,000 and 144,000. The white-cell count, which was 10,500 on admission, rose to 12,200 after 3 weeks, and was 9,400 on discharge. On the day following admission, the differential count was 48 per cent neutrophils, 24 per cent lymphocytes, 26 per cent eosinophils and 1 per cent basophils. The eosinophilia remained high for the first 2 1/2 weeks and then fell to within normal limits. More detailed studies of the peripheral blood are presented in Table 1.

Bone-marrow examinations were performed* on May 13 and 24 and July 28 (Fig. 1, 2 and 3), the first two of which

limeter, and the total protein was 40.76 mg, and the sugar 78 mg per 100 cc, and the chloride 119 milliequiv. per liter. Heterophil-antibody agglutination was negative. The stools were guaiac negative.

X-ray study of the chest revealed the heart to be normal in size, shape and position. The aorta was slightly elongated and tortuous. Both lung fields showed diffuse fibrosis and emphysema. X-ray examination of the abdomen on May 12 demonstrated a normal amount of gas in the bowel. Both kidneys were of normal size, shape and position. The out-

*Bone marrow studies and examinations of the peripheral blood were performed by Dr. Charles Emerson, Robert Dawson Evans Memorial Massachusetts Memorial Hospitals.

lines of the psoas muscles were clear. An x-ray film of the skull revealed no fracture.

The clinical course is demonstrated in Figure 4. The patient was treated with a high-carbohydrate, high-protein, high-vitamin diet with supplementary vitamin B preparations. The temperature during the first day was 100 to 100.4°, and by the 3rd day it fell to 99.0° and thereafter was normal. The pulse was never above 92. The patient was given 150,000 units of penicillin daily from the 6th to the 17th day. During the first 2 days he was lethargic, and hiccups were almost continuous. Hiccups stopped after the 5th day, and beginning clinical improvement was noted. The rash remained hemorrhagic for the first 5 days and then slowly faded. Desquamation started on the 5th day and gradually extended over the entire body. By the 13th day the liver had decreased

and careful clinical observation), tridione remains the most effective treatment currently available for petit mal epilepsy.* This opinion is supported by the experience of Dr. William G. Lennox, who has treated large numbers of children with tridione, has taken necessary precautions and has encountered little serious toxicity.

The case presented above indicates that tridione is potentially toxic to the liver also, and may stimulate the bone marrow as well as depress it. It sug-

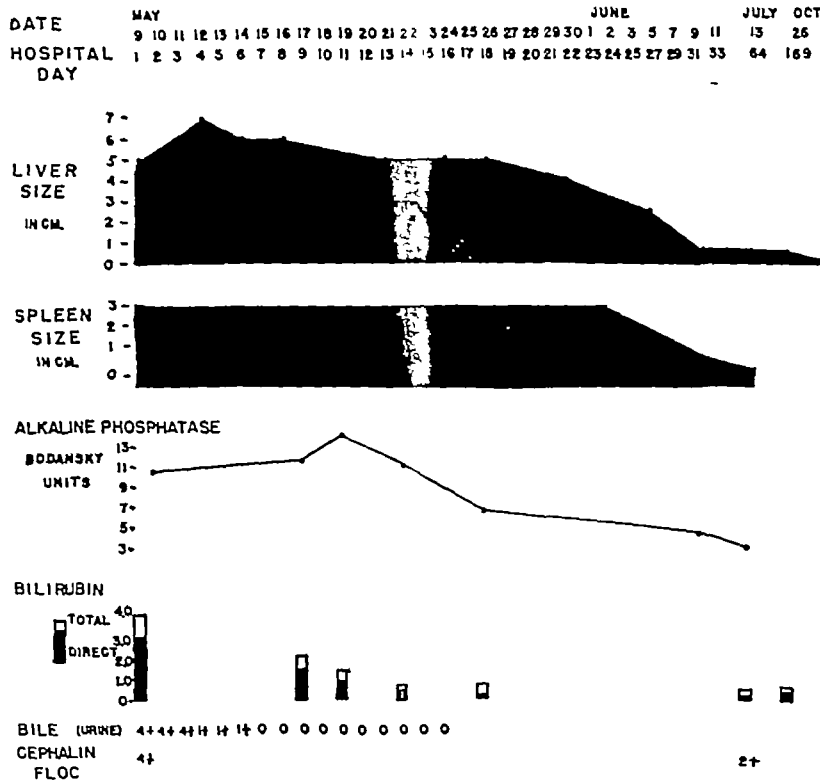


FIGURE 4. Clinical Course

in size, the edge being felt 1 cm to 4 cm below the costal margin. After the 32nd hospital day the spleen was never palpable. The enlargement of the cervical and axillary lymph nodes gradually subsided so that at the time of discharge they were insignificant. The patient was discharged on June 11, improved. Follow-up study revealed that liver function, as well as his general condition, had gradually improved.

DISCUSSION

Tridione, a comparatively new anticonvulsant drug, has been found to be an effective agent in the treatment of petit mal seizures. It has not been shown to be effective in other forms of epilepsy. It has been demonstrated further to be potentially toxic to skin, bone marrow, and kidneys. If this is anticipated and the proper precautions taken (frequent peripheral-blood and urine examinations

gests also the extreme need for careful diagnosis before tridione is used, since it appears to be effective only in petit mal attacks, whereas this patient had sensory (epigastric) seizures. Petit mal epilepsy is characterized by an onset of unconsciousness, brief in duration, without aura, at times with akinetic or myoclonic features. An attack, no matter how brief, that begins with any aura other than unconsciousness is not petit mal.¹⁴ This case indicates further that tridione should not be used unless careful supervision is maintained throughout.

The toxic hepatitis in this patient responded very well to the usual treatment of hepatitis—

*Paradione (3,5-dimethyl-5-ethyl-oxazolidine-2,4-dione), a new experimental derivative of tridione, has been found in the early experience of one of us (I.C.H.) to be at least as effective as tridione and considerably less toxic.

membranes were injected. The tongue was dry and coated. No distention of the jugular veins was apparent. The chest was clear to percussion and auscultation. The left border of cardiac dullness was 8.5 cm from the midsternal line in the 5th interspace. There was normal sinus rhythm. The liver was palpable and slightly tender, and the edge was felt 7 cm below the right costal margin on inspiration. The spleen was palpable 3 cm below the left costal margin. Peristalsis was normal. A right reducible inguinal hernia was present. The prostate was moderately enlarged. Neuro-

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logic examination was negative except for absent patellar and Achilles-tendon reflexes bilaterally.

The temperature was 100.2°F (by rectum), the pulse 88, and the respiratory rate 18, the blood pressure was 125/75.

The urine showed a specific gravity of 1.006 to 1.022 and gave a +++ to ++++ test for bile. The urobilinogen was 1.16 on many occasions. Slight traces of albumin were noted in the sediment on several occasions. Bile was present for the first 6 days. Blood studies showed a sedimentation rate of 12 mm per hour on admission, which rose to 47 mm in the 3rd week and then fell to 30 mm prior to discharge. The hematocrit was 49 per cent on admission and 34 per cent on discharge. The blood Hinton reaction was negative. The hemoglobin was 15.5 gm on admission and 11.9 gm on discharge. The reticulocyte count was 0.7 per cent, and the platelet count 173,000 and 144,000. The white-cell count, which was 10,500 on admission, rose to 12,200 after 3 weeks, and was 9400 on discharge. On the day following admission, the differential count was 48 per cent neutrophils, 24 per cent lymphocytes, 26 per cent eosinophils and 1 per cent basophils. The eosinophilia remained high for the first 2 1/2 weeks and then fell to within normal limits. More detailed studies of the peripheral blood are presented in Table 1.

Bone-marrow examinations were performed* on May 13 and 24 and July 28 (Fig. 1, 2 and 3), the first two of which

*Bone-marrow studies and examinations of the peripheral blood were performed by Dr. Charles Emerson, Robert Dawson Evans Memorial Massachusetts Memorial Hospital.



FIGURE 3 Sternal Marrow on July 28 (x 400)

The degree of proliferation and composition of the marrow is completely within normal limits, myelocytes and metamyelocytes now constituting approximately a third of the leukocytes present.

limeter, and the total protein was 40.76 mg, and the sugar 78 mg per 100 cc, and the chloride 119 milliequiv. per liter. Heterophil-antibody agglutination was negative. The stools were guaiac negative.

X-ray study of the chest revealed the heart to be normal in size, shape and position. The aorta was slightly elongated and tortuous. Both lung fields showed diffuse fibrosis and emphysema. X-ray examination of the abdomen on May 12 demonstrated a normal amount of gas in the bowel. Both kidneys were of normal size, shape and position. The out-

epidemiologic data at the end of the 1933 epidemic, Leake et al.² reported that either mosquitoes were involved as vectors, or the infection was spread by contact. Mosquito transmission in the laboratory was attempted at that time but failed.² Since the original outbreak in St. Louis, other encephalitis epidemics have been recognized as predominantly due to this virus,^{3, 4} and there have been mixed St. Louis and western equine outbreaks.^{5, 5-10} Interesting to note with this is that horse infections, both of clinical and of inapparent nature, have been produced by the inoculation of the St. Louis virus.¹¹⁻¹³ Antibodies to the St. Louis virus have been found in the serums of normal persons and of those convalescent from encephalitis in many parts of the United States and even in Africa.^{3-10, 14-17} Antibodies have also been demonstrated in the serum of horses and of numerous other vertebrates, both domestic and wild.^{8, 9, 12, 16, 18-21} Blattner and Heys² reported the occurrence of 10 to 16 cases each year in the St. Louis area during the nonepidemic years 1939-1944, with a total of 88 cases during the seven-year period, and postulated the presence of an endemic focus.

In recent years, various investigators working both in the field and in the laboratory have established the mosquito as the vector. Hammon, Reeves et al. isolated the St. Louis virus from eight pools of naturally infected *Culex tarsalis* mosquitoes from the Yakima Valley, Washington, 3 in 1941,^{22, 4} in 1942,²⁴ and 1 in 1944.²⁴ Also, a strain was isolated from *C. pipiens* (Linnaeus) caught in Washington in 1942,²⁴ and a strain was isolated in 1944²⁴ from *Aedes dorsalis* (Meigen) caught in Kern County, California. The latter was the first isolation of the St. Louis virus from any source in California even though serologic evidence of the presence of the virus had been repeatedly obtained.^{5, 10, 25} Although no tests of the vector ability of *A. dorsalis* had been made in the laboratory, transmission had been demonstrated by four other species: *A. lateralis* (Meigen), *A. taeniorhynchus* (Wied), *A. vexans* (Meigen) and *A. nigro-maculis* (Ludlow).²⁶ A Japanese report in 1940²⁷ recorded the transmission of the St. Louis virus by *C. tritaeniorhynchus* (Giles) and *A. albopictus* (Skuse), in addition to the previously reported *C. pipiens* (var. *pallens* Coq).

Studies on the feeding habits of the suspected mosquito vectors in Washington,²⁸ Nebraska²⁹ and California³⁰ confirmed the fact that the two *Culex* mosquitoes found infected fed predominantly on fowl. Detailed studies³¹ on inoculated chickens in 1945 showed that a very high dilution of St. Louis virus, representing only a 50 per cent end-point dose for a mouse by the intracerebral route, when inoculated subcutaneously gave rise regularly to virus in blood in a titer greater than that inoculated, usually for two or three days. No mammal tested up to that time had proved to be as good a potential source of mosquito infection.

In spite of this apparently satisfactory and well established concept of the mosquito-fowl-mosquito cycle, the epidemiology of this disease seemed to be incomplete, for the chicken and other birds tested showed no evidence of serving as chronic or latent carriers of the virus. Hibernating *C. tarsalis* and *C. pipiens* collected during winters in Washington²² and California³⁰ had not been found infected even though 5429 mosquitoes were tested. Furthermore, eggs and progeny of infected *C. tarsalis* and *C. pipiens* were tested only to yield no evidence of transovarian passage of the virus. Therefore, knowledge of the true reservoir and the location of the virus during the winter and during seasons of no apparent infection was still quite vague.

It had been postulated that the true reservoir for the virus was either a vertebrate or an arthropod. A wide variety of vertebrates inoculated by the dermal routes failed to yield results suggesting a true reservoir. Blattner and Heys,²² in 1944, however, found that *Dermapentor variabilis* (Say) was capable of transmitting the infection and of passing it on to its progeny, thereby suggesting a potential reservoir. However, no naturally infected ticks have been found, nor have any of the stages of *D. variabilis* been found upon fowl. In 1945, Smith, Blattner and Heys³² isolated the St. Louis virus on three different occasions from chicken mites (*Dermanyssus gallinae*, De Geer). Working on the hypothesis that mites and ticks belong to the same order of arthropods and are known to transmit other pathogenic agents transovarially, these investigators demonstrated in 1947 the transovarian transfer of infection by mites infected with the virus.³⁴ Furthermore, the virus was isolated from chickens exposed to infected mites, and fresh mites feeding on infected chickens became infected.

It is now generally accepted that the St. Louis virus is frequently transmitted to man by mosquitoes that have become infected, in most cases by feeding on recently infected fowl. However, the true reservoir or winter carry-over mechanism has still not been definitely ascertained. Other ectoparasites of birds, such as ticks and mites, may be the unknown factor.

AMERICAN EQUINE ENCEPHALITIDES

In Horses

For many years in Europe a mild form of equine encephalomyelitis of horses has been known as Borna disease. The causative agent was demonstrated to be a filterable virus in 1924.³⁵ Similar symptoms have been observed among horses for a number of years in the United States. The Kansas-Nebraska horse plague of 1912 was probably a related disease. However, the first recognized American epizootic of horses similar to this condition occurred in the San Joaquin Valley of California in 1930 when the identity of the disease was established by Meyer, Haring and Howitt,³⁶ who isolated

namely, bed rest and high-carbohydrate and high-protein diet, together with added vitamin supplements, especially of the vitamin B complex. Early recognition and vigorous treatment of any of the toxic complications of tridione may save the life of the patient.

SUMMARY

The case of a sixty-nine-year-old man who exhibited toxic hepatitis, a leukemoid bone-marrow reaction and a severe exfoliative dermatitis after tridione therapy is reported. A review of the literature concerning the adverse reactions to the drug is presented. Suggestions concerning the use of tridione are made.

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MEDICAL PROGRESS

PUBLIC-HEALTH ASPECTS OF THE VIRUS ENCEPHALITIDES

JOHN C. AYRES, M.D.,* AND ROY F. FEEMSTER, M.D., DR.P.H.†

BOSTON

VIRUS encephalitides are best discussed in three groups: virus encephalitides caused by familiar viruses not ordinarily encephalitogenic, suspected, primary virus infections, and primary virus infections.

Virus encephalitides can be caused by ordinarily nonencephalitogenic viruses, which are those of herpes simplex, measles, lymphogranuloma venereum, mumps and infectious mononucleosis (probably due to a virus). Although secondary or post-infectious encephalitis has not as yet been shown to be caused by a virus, the illness occurs within a few days to a few weeks after various virus infections, such as measles, mumps, influenza, chicken pox, vaccinia, smallpox and infectious hepatitis and after vaccination against smallpox and rabies.

Suspected primary virus encephalitides are newly discovered, and their role is significant because antibodies have been found in the blood of man, and the viruses are neurotropic in laboratory animals. Clear-cut clinical infections of the encephalitic type are yet to be seen. The viruses are West Nile, Bwamba fever, Semlike forest, Bunyamwera and Hammon-Reeves, California. The first two have been recovered from the blood of man, and the remainder from mosquitoes only. Other sus-

pected primary virus encephalitides are von Economo's disease and acute disseminated encephalomyelitis although their virus etiology has not as yet been established.

The primary virus encephalitides are the St. Louis type of encephalitis, eastern equine encephalomyelitis, western equine encephalomyelitis, Venezuelan equine encephalomyelitis, Japanese B encephalitis, Russian Far East (tick-borne, spring-summer) encephalitis, acute hemorrhagic meningoencephalomyelitis (leukoencephalitis), lymphocytic choriomeningitis, pseudolymphocytic choriomeningitis, swineherd's disease, louping ill, acute encephalitis due to rabies and the Sabin B virus. The first six are known as the summer, or epidemic, encephalitides, the remainder are endemic virus encephalitides.

The epidemic encephalitides are a greater public-health problem than most of the others. They tend to be more numerous and present difficult problems in control, because the reservoir of the virus is usually a lower animal and the viruses are spread to man by arthropod vectors. This paper is limited to a discussion of these six virus infections.

ST. LOUIS ENCEPHALITIS

The St. Louis epidemic of 1933¹ was up to that time the largest localized encephalitis epidemic recognized in North America. In summing up the

*Epidemiologist, Division of Communicable Diseases, Massachusetts Department of Public Health.

†Director, Division of Communicable Diseases, Massachusetts Department of Public Health.

virus of eastern equine encephalomyelitis Hammon et al isolated the western type from free living *C. tarsalis* five times in 1942²³⁻²⁶ and forty-one times in 1943²⁴ from collections made in the Yakima Valley, Washington, twenty-eight times from the San Joaquin Valley, California, in 1943²⁰ and once from eastern Nebraska in 1943²⁹ Kitzelman and Grundman⁷⁰ recovered the western type virus in 1940 from a cone-nosed bug (*Triatoma sanguisuga*, Le Conte) in Kansas Sulkin, in 1945,⁷¹ reported the recovery of the western virus from the chicken mite, *Dermanyssus gallinae*, and Reeves et al, in 1947,⁷² recovered the western type from wild bird mites (*Liponyssus sylviarum*) in California Syverton and Berry⁷³⁻⁷⁴ have been able to transmit the western virus by ticks (*Dermacentor andersoni*)

Significant findings have directed attention toward fowl, both wild and domestic, as representing the most common intermediate host in the cycle of infection⁷⁵ Repeated isolations of both eastern and western strains of virus from various species prove that they may experience a specific infection usually of a mild or subclinical nature⁶⁹⁻⁷⁰⁻⁷⁶⁻⁸² Overwhelming evidence of incriminating fowl as the major inapparent reservoir has been advanced by the large-scale serum surveys of Howitt,⁵⁻⁵³ Howitt and van Herick²¹⁻⁵⁴ and also Hammon and his associates³¹ The serologic evidence suggests strongly that, in Washington and California, infection rates with western equine encephalomyelitis are higher in birds than in mammals In these areas, the chick has frequently been found to possess antibodies, and since it can easily be infected experimentally, it is thought to be one of the principal sources of mosquito infection if not a true reservoir or latent carrier However, in Nebraska no antibodies were detected in any of the chickens or pheasants tested In Texas only 8.5 per cent of the domestic fowl were positive for western equine antibodies²¹ Cox, Jellison and Hughes⁵⁰ found an infected deer in North Dakota in 1941, and McNutt and Packer³⁵ an infected hog

Recovery of viruses from species of mosquitoes habitually feeding on avian hosts has established the significance of the mosquito-fowl-mosquito cycle of infection, man or horse representing merely the accidental host However, insect vectors and also the reservoirs of infection may differ from one section of the country to another Furthermore, as with St. Louis encephalitis, the winter carry-over mechanism has still to be definitely ascertained, although the isolation of the western type of virus from mites capable of transovarian transmission may be the answer

VENEZUELAN EQUINE ENCEPHALOMYELITIS

Kubes and Rios⁵⁶ and Beck and Wyckoff³⁷ isolated a virus from cases of equine encephalomyelitis from Venezuela in 1938 The infection had been recognized also in Colombia,⁵⁵⁻⁵⁹ Ecuador⁷⁵ and

Trinidad⁹⁰⁻⁹¹ Several early reports reviewed by Gallia and Kubes⁹² suggest that cases may have occurred in man in the epidemic areas In 1943, 2 fatal cases, with subsequent isolation of the Venezuelan virus from brain tissue, were recorded⁹¹⁻⁹³ One of the cases preceded⁹¹ and the other occurred during⁹³ an epizootic among horses and mules in Trinidad, B. W. I. In 1942 mild infections developed in 2 laboratory workers in New York⁹⁴ and in 1943, 3 laboratory workers in Rio de Janeiro had a similar illness⁹⁵ Gallia and Kubes,⁹² examining the sera of 10 laboratory workers at the Institute of Veterinary Research in Caracas, Venezuela, found high titers of neutralizing antibody against the virus in 10 of 10 persons, only 1 of the 10 having typical symptoms

Epidemiologically, mosquitoes have been incriminated in the natural equine infections with this virus,⁹⁶ and several potential vectors have been demonstrated⁹⁶⁻⁹⁷ Gilvard found *Mansonia titilans* (Walker) infected in Trinidad and demonstrated experimental transmission with the same species⁹⁶ Spread probably occurred from Ecuador to Trinidad, and it is easy to conceive of its spread by ship or plane or by island hopping to the Gulf Coast of the United States, where *Mansonia titilans* is already present

In the New York and Brazilian reports,⁹⁴⁻⁹⁵ the virus was isolated from the blood of 7 of the 10 laboratory cases (5 on the second day of illness, 1 on the third, and 1 on the fifth) Virus was also isolated from the nose or throat washings in 2 cases (both on the second day of illness) Koprowski and Cox,⁹⁸ in 1947, reported 4 cases of laboratory infection, in 2 of which there had been no direct contact with the virus prior to infection Furthermore, the virus was isolated from the circulating blood in 3 cases and from the throat washings in 1

JAPANESE "B" ENCEPHALITIS

The name Japanese "B" encephalitis was originally used to distinguish it from the von Economo type, which the Japanese called type "A" The former is an epidemiologically and clinically distinct type of epidemic encephalitis that frequently occurred in Japan in the late summer It has probably occurred in epidemic form in Japan proper since the beginning of this century, or quite possibly even thirty years previously However, not until the great epidemic of 1924, involving over 6000 persons with 3797 reported deaths, did it attract much attention Since then, annual epidemics have been recorded, sometimes from numerous regions Between 1924 and 1937, from Japan alone, 21,355 cases with 12,159 deaths were reported⁹⁹ Case mortality rates have ranged from 42 to 74 per cent, but have averaged about 60 per cent Epidemics or sporadic cases have also been reported from Formosa,⁹⁹ the southern Ryukyu Islands,⁹⁹ eastern China¹⁰⁰⁻¹⁰¹ and the eastern part of the

a filterable virus from the brain of 2 horses that had died from the disease. The virus was found to be immunologically different from that of Borna disease and became known as the western variety of the equine encephalitis virus.

During the early 1930's, the disease extended rapidly eastward, recorded cases reaching the peak numbers of 173,589 in 1937 and 184,062 in 1938.¹⁷ In 1939 the western type of virus was found as far east as Kentucky, and in 1940, it was identified in Alabama,¹⁸ and in 1941, in Michigan.¹⁸ Up to 1944 the western type of virus had been identified in 19 states.^{18, 19}

In 1933 a highly fatal form of encephalomyelitis appeared in several states along the Atlantic Coast, particularly New Jersey and Virginia. The virus from these equine cases was found to be different immunologically from the previously isolated western strain²⁰ and was therefore designated as the eastern type of virus. In 1940 it was identified in Alabama,¹⁸ in 1941, in Texas,²¹ in 1942, in Michigan,¹⁸ and in 1944, in Louisiana and Missouri.¹⁸ Up to 1944 the states from which eastern virus had been identified totaled 15. Thus, it became apparent that the eastern virus was no longer confined to the eastern seaboard but had spread to involve the Gulf Coast states, Michigan and Missouri. Furthermore, both eastern and western types have

In Man

Karl Meyer,²² in 1932, was the first to suspect that an unusual encephalitis contracted by men working with infected horses might be due to the virus of equine encephalomyelitis. Examination of the brain of a ranch hand who died of the disease showed pathologic lesions similar to those observed in horses, however, this clinical impression was not proved by isolation of the virus or by the presence of neutralizing antibodies in the serum of the infected persons.

In August, 1938, an epizootic of considerable proportions occurred among horses in southeastern Massachusetts. At about the same time a very fatal type of encephalitis among infants and children made its appearance in the area. From a child dying in the Children's Hospital of Boston, Fothergill and his associates²³ isolated a virus that was identified by cross-protection tests as the virus of eastern equine encephalomyelitis. This was confirmed for the same case and 4 others by Webster and Wright,²⁴ who used the complement-fixation test. In patients who recovered Fothergill confirmed the diagnosis by neutralization tests. During the same month Howitt²⁵ isolated the virus of the western type from the brain of a twenty-month-old child dying in California. Furthermore, the blood of several persons in California who had recovered from encephalomyelitis was shown to contain neutralizing antibodies for the western virus. Thus, it was established that both known American types of equine encephalomyelitis could infect man.

Since then, the Manitoba (Canada),²⁶⁻²⁸ Minnesota and Dakota epidemics of 1941,^{29, 30} and the annual outbreaks in the Yakima Valley^{31, 32, 33} and in Kern and Fresno counties in California^{34, 35} have attested to the ever-increasing importance of this disease. The 1941 epidemic in and around North Dakota was the largest ever recorded, with 1080 cases and 90 deaths.³⁶ In Manitoba that same year, 509 cases were recognized.³⁶ In all the areas mentioned above, the western virus was found to be the causative agent. During 1941 in Texas an epidemic of the eastern type occurred, during which repeated isolations of the virus were made from horses,^{37, 38, 39} and a number of probable human cases were later revealed by mass serologic studies.^{17, 39, 40}

Transmission

In 1933, Kelser⁴¹ first proved that the virus of equine encephalomyelitis could be transmitted by the mosquito *A. aegypti*. In the succeeding few years, several workers⁴²⁻⁴⁵ confirmed the work of Kelser definitely incriminating the Aedes as potential carriers of both eastern and western type of equine encephalomyelitis. Davis,⁴⁶ in 1941, reported on the ability of five species of Aedes mosquitoes native to Massachusetts to transmit the

TABLE 1 Distribution of Equine Encephalomyelitis in the United States, 1933-44*

WESTERN TYPE	EASTERN TYPE	BOTH TYPES
Alabama	Alabama	Alabama
Arizona	California	California
California	California	California
Colorado	Colorado	Colorado
Florida	Florida	Florida
Georgia	Georgia	Georgia
Illinois	Illinois	Illinois
Iowa	Iowa	Iowa
Kansas	Kansas	Kansas
Kentucky	Kentucky	Kentucky
Michigan	Michigan	Michigan
Minnesota	Minnesota	Minnesota
Missouri	Missouri	Missouri
Nebraska	Nebraska	Nebraska
Nevada	Nevada	Nevada
North Dakota	North Dakota	North Dakota
South Dakota	South Dakota	South Dakota
Texas	Texas	Texas
Utah	Utah	Utah
Washington	Washington	Washington

*Based on data of Slaughter and Glaser.⁴⁷

been identified in Michigan, Texas and Alabama (Table 1).

The countries adjoining the United States have had the same immunologic types of virus that are known to occur in this country. The western virus has prevailed in Canada, except for a limited number of sporadic cases due to the eastern virus in Ontario.^{48, 49} The western virus has been identified in Argentina,^{50, 51} whereas the eastern virus has been reported from Mexico,⁵² Panama,⁵³ Brazil^{54, 55} and Cuba.⁵⁶

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Soviet Union¹⁰² Smithburn and Jacobs¹⁷ stated that, as a result of serologic tests, "the St. Louis and Japanese 'B' viruses have been active over broad expanses of territory in Central Africa," and Sabin¹⁰³ in 1943 reported a number of positive serologic tests for Japanese "B" virus in the Cincinnati area.

In the summer of 1945, an epidemic of encephalitis occurred among the native population on Okinawa and the adjacent islands¹⁰⁴ and was diagnosed as being of the Japanese "B" type by the complement-fixation test¹⁰⁵. A total of 127 cases was found. However, it was believed that this number may have represented only 15 to 30 per cent of the total¹⁰⁶ because special conditions precluded discovery of all cases. At the same time, there were 38 cases of suspected virus infection of the nervous system among the American military personnel.¹⁰⁷ A definite clinical diagnosis of encephalitis was probably justified in only 12 of the cases, but a specific serologic diagnosis was established only in 9 and a diagnosis by other methods in 2 fatal cases.

This outbreak gave an excellent opportunity for the study of the epidemiology of the Japanese "B" encephalitis. Following the pattern of the work done on St. Louis and Western Equine Encephalitis, a search for vertebrate hosts infected with Japanese "B" virus was made. Horses, a cow and 3 goats were found to have neutralizing antibodies,¹⁰⁷⁻¹⁰⁸ but none of the chickens taken from the epidemic area showed evidence of infection. Furthermore, either few or no mites could be found on these or other chickens in the encephalitis zones.

Japanese¹⁰⁹ and Russian¹¹⁰ investigators have reported the isolation of Japanese "B" encephalitis virus from *C. tritaeniorhynchus* and *C. pipiens* (var. *palleus*) mosquitoes caught in nature. These mosquitoes as well as *A. togoi*, *A. albopictus* and *A. japonicus*¹¹¹⁻¹¹² were demonstrated experimentally to be potential vectors. Reeves and Hammon,¹¹² in 1946, further showed the ability of six species (*C. quinquefasciatus*, *C. tarsalis*, *A. dorsalis*, *A. nigromaculis*, *Culiseta incidens* and *C. inornata*) of the California mosquitoes to transmit the Japanese "B" virus to animals and have demonstrated the presence of the virus in the blood of inoculated chickens.¹¹³ Domestic animals have also been infected experimentally.¹¹⁴ Fear has been expressed that, once introduced into any areas where the American types of encephalitis now propagate, the Japanese "B" encephalitis might become a "greater plague than any we have at present."

Before and during the Okinawa epidemic of 1945, *C. quinquefasciatus* was in abundance and most readily found¹⁰⁷, however, tests on three pools did not yield any virus, nor were any chickens, which are known to be bitten by this mosquito in the United States, found infected. It was postulated, therefore, that some other mosquito, biting larger domestic animals and human beings, was a vector

on Okinawa. The real reservoir of the virus was not found, and it was again suggested that the vertebrate hosts and possibly the invertebrate vectors varied from one area to another.

RUSSIAN SPRING-SUMMER ENCEPHALITIS

For the past forty years, at least, an epidemic type of human encephalitis has been occurring annually in the forest regions of the Far East, Siberia and the European part of the Soviet Union, the Urals, Karelia, West Ukraine and White Russia. It occurs only during the spring and early summer, coinciding with the activity of ticks. Russian investigators have reported the isolation of the etiologic virus from man, rodents and ticks.¹¹⁵⁻¹¹⁹ They have also demonstrated conclusively the tick-wild-animal-tick cycle and the tick-tick transovarian cycle, with man as an accidental or incidental host.

Studies on the virus itself made in this country by Casals and Webster¹²⁰⁻¹²¹ have shown it to be very similar or identical with the virus of louping ill of sheep in Scotland, also known to be tick borne. Silber and Shubladse¹²² reported in 1945 that louping ill is the tick-borne encephalitis of the western part of the Soviet Union, but that a different virus is responsible for the tick-borne encephalitis in the far eastern area. The tick is both a vector and a reservoir so that accidental transportation of infected ticks, as has already been accomplished for experimental purposes,¹²¹ might easily establish this infectious agent in the tick areas of the United States.

LABORATORY DIAGNOSIS OF THE ENCEPHALITIDES

Virus neutralization and complement-fixation tests are important not only because they can be used diagnostically to establish the titer of antibody in blood but also to determine the prevalence of the disease and the geographic dissemination of its virus. With a known virus, its specific antibody can be demonstrated, and with a known antibody, the identity of a virus can be revealed.

Neutralization Test

The presence of significant amounts of neutralizing antibody indicates previous infection by a virus, even though there may have been no apparent disease. This factor is the basis of the "two or three phase" test. Under ideal conditions, a specimen of serum obtained as early as possible during the acute phase of illness, another one or two weeks after onset, and a third, if necessary, taken still later, three to eight weeks after onset, are subjected to the neutralization test. Since infection by a virus may be clinically inapparent, normal persons may show specific neutralizing antibody.⁶⁷⁻¹²³⁻¹²⁵ hence, a single positive specimen may be misleading, especially if the person has lived in endemic areas. The reason for selecting the intervals from the earliest time to eight weeks after

onset for test is that this antibody appears at varying times after infection with different viruses. In western equine virus infections, neutralizing antibody appears as early as the fourth day after onset, and in St Louis and Japanese "B" encephalitis from three to seven days to as late as three weeks.

The success of virus neutralization as a diagnostic procedure depends upon the precision with which, in the comparison of serums obtained in the acute and convalescent stages of infection from the same patient, a definite increase of antibody in the later sample is revealed. To measure this increase in antibody (or in the protective power of an antiserum), one of two methods may be used. Undiluted serum is tested against varying quantities of virus¹²⁶, or graded dilutions of serum against a specific quantity of virus¹²⁷.

There are two choices of laboratory recipients for serum-virus mixtures when the neutralizing capacity of a serum is to be tested: the serum-virus mixtures are injected into an animal that is uniformly and highly susceptible (that is, for encephalitis viruses, generally the albino mouse), or the mixtures are injected into developing chick embryos¹²⁸. As a rule, the latter technic merely supplements the former or is used only for special purposes.

The specificity of the neutralization of a virus by its antiserum is generally accepted. However, there are records of cross reactions, but these occur between viruses that have common characteristics, which are reflected by common antigenic complexes. The cross reactions (also encountered in complement-fixation tests) between West Nile, St Louis encephalitis and Japanese "B" encephalitis viruses indicate a relation of the three infections¹²⁹⁻¹³¹. The serologic cross reactions are not pronounced, and laboratory workers circumvent this obstacle by utilizing the fact that the homologous reactions are usually at a definitely higher level, especially when the virus antibody mixture is injected intraperitoneally or subcutaneously. More decided cross reactions (neutralization, complement fixation) occur between louping ill and Russian Far East encephalitis viruses. However, homologous titers are always higher and cross-resistance tests by intracerebral injection exhibit definite differences between the two.

Complement-Fixation Test

Prior to 1937, several workers attempted to apply the complement-fixation reaction to the study of neurotropic viruses. The results were unsatisfactory owing to a lack either of specificity or of appropriate controls. The material from which the complement-fixing antigens are derived consists of tissue extract in which the extraneous material sometimes outweighs the specific antigen. This extraneous material can mask the results of the test, either by its anticomplementary effect or by its capacity of combining with test serums

to produce nonspecific reactions. In 1941 Casals and Palacios¹³² demonstrated the practicability of the test for diagnosis of several neurotropic viruses, using brain-tissue suspensions as a source of antigen. Their method is still employed, with some modifications, and consists of emulsifying infected mouse brain tissue and then centrifuging it. The supernatant is then alternately frozen and thawed until flocculation takes place, when it is centrifuged again. This supernatant contains the antigen, which is highly virulent and can be inactivated by ultraviolet irradiation¹³³ or by heating at 60°C for thirty minutes¹³⁴. Other methods of preparation of antigen are the low-speed centrifugation of infected chick embryos with inactivation by ultraviolet radiation¹³⁵ and the extraction with benzene from infected chick embryos or mouse brains with inactivation by 0.05 per cent formalin¹³⁶.

In preparation of animal hyperimmune (positive control) serums, it was found that the injection of tissue extracts derived from one animal species into another animal species made possible the development of confusing species or organ-specific antibodies¹³²⁻¹³⁷⁻¹³⁸. Fortunately, the tissue component responsible for nonspecific reactions¹³⁹ was found sedimentable at 20,000 r.p.m. In some species this antibody-like substance is thermolabile,¹³²⁻¹³³ being totally destroyed at 65°C.

It was also found that human Wassermann-positive serums gave, as a rule, a nonspecific reaction with brain extracts¹³² and benzene-extracted antigens¹³⁶, however, this is overcome by heating of the serums at 65°C for twenty minutes.

Since this information became available, the complement-fixation test has become a more satisfactory test for diagnosis of neurotropic virus diseases. However, it has not as yet been accepted for general use as has the neutralization test.

Obtaining and Sending Serum to be Tested

Persons should be bled for test serum after several hours of fasting (usually in the morning before breakfast) and with sterile technic. After 20 cc of blood is withdrawn, it is allowed to stand for half an hour at room temperature and to clot. Then, after having been centrifuged at 2500 r.p.m. for twenty minutes, clear serum is pipetted off. If a preservative is necessary a 1:50,000 dilution of phenyl mercuric borate can be added (or 1:2,500 borate stock, 1 drop to each 1 cc of serum, as an estimate). The serum is placed in a hard glass ampoule, which is sealed. If a test tube is used, it should be closed with a cork or rubber stopper, and the top should be completely waxed. A glass container should be filled only to a third of its volume to prevent bursting during freezing. The container is kept at about -76°C by carbon dioxide snow until tested. It should be sent to the designated laboratory by the fastest method, preferably in a vacuum jar holding solidified carbon dioxide. If this refrigerant is not available, the

serum should be sent fluid, provided it can reach its destination within thirty-six hours

PREVENTION OF VIRUS ENCEPHALITIDES

Prevention in this group of diseases consists of vector control and vaccination. With so many species of animals and birds susceptible to the viruses and with the disease occurring among them in nature, control of the primary and secondary hosts is difficult. However, much can be done in the way of vector control on a community-wide scale, and individually. Since the mosquito is apparently the major vector, modern mosquito-control procedures on a community basis should afford some protection during an outbreak. Also, individual measures, such as adequate screening of houses, avoidance of exposure to mosquitoes, and the use of new insecticides and repellents, should be carried out during an epidemic.

The observation of Higbie and Howitt,¹⁴⁰ in 1934, that equine encephalomyelitis virus may be cultivated in ten-day-old developing chick embryos provided the basis for subsequent work^{141, 147} on the preparation of formalin-inactivated vaccines effective in establishing active immunity in horses and mules. The earlier vaccines had consisted of inactivated virus in suspensions of brain tissue from animals infected with the appropriate virus.

Although such vaccines are satisfactory for administration to horses, their high content of chick tissue and egg components makes them potentially dangerous as human prophylactic agents. From 1941-1943, approximately 6103 persons were vaccinated in Manitoba against western equine encephalomyelitis, with relatively mild reactions in general and no fatal results.^{58, 124, 125} During the outbreak of Japanese "B" encephalomyelitis on Okinawa in 1945, 60,000 to 70,000 military personnel received mouse brain vaccine with only three reports of a form of "neuritis" of a questionable character and 19 allergic reactions suggesting sensitivity to formaldehyde.

In the following summer, 250,000 additional persons were vaccinated with only three reports of infectious polyneuritis, which was in no way different from that occurring among unvaccinated personnel in the Far East.¹⁴⁷ Furthermore, the Russians have effectively used a formalinized tissue vaccine to protect man in epidemic areas.¹⁴⁸

Randall et al.,¹⁴⁹ in 1947, prepared a purified formalinized vaccine against eastern, western and Venezuelan viruses and demonstrated upon guinea pigs active immunity against homologous types of virus, even when injected directly into the brain. Moreover, antibodies neutralizing the eastern virus were demonstrated in the serums of guinea pigs after the administration of the eastern type of vaccine and in the serums of human beings after the injection of a mixture of eastern and western types of vaccine. Usually two doses are given a week

apart and neutralizing antibodies appear one or two weeks after the first inoculation. These injections should be given annually.

There is seldom valid reason to recommend the vaccination of the entire group of susceptible human beings in a community against encephalitis. Anyone who, by reason of his work, must be heavily exposed to mosquito bites in an epidemic area should be permitted the protection of the vaccine. However, whether general or extensive vaccination of the most susceptible groups (infants and those over fifty) or military personnel is advisable should be decided by those in charge of public-health administration who can weigh various factors involved in any particular area or group.

Constant vigilance has been maintained in Massachusetts since the outbreak of 1938 to detect additional cases of encephalitis due to the eastern virus. No additional cases have been discovered. No proved cases in horses have been found since 1939.

It is suspected that optimum conditions occurring in the Commonwealth in 1938 favored the spread of the virus from the reservoir host (as yet undetermined) to horses and to man. Certainly the suspected mosquitoes were present in abundance.

It is probable that another outbreak will not occur until the virus again builds up in a reservoir host simultaneously with an unusual abundance of the necessary mosquito vector. The information accumulated in the 1939 state-wide mosquito survey will then be put to practical use.

SUMMARY

The public-health aspects of the six most important viruses that cause epidemic encephalitis are discussed, including the characteristics of the etiologic agents, their possible reservoirs, the usual vectors, the laboratory diagnosis and the possible means of control.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 35241

PRESENTATION OF CASE

First admission A twenty-six-year-old salesgirl was admitted to the hospital complaining of amenorrhea and swelling of her left leg.

Nine years before admission an appendectomy was performed at another hospital. Following the operation she developed swelling of the left leg. This continued up to admission, and was more severe after standing for long periods. Five years before admission the patient's twin sister, upon whom the patient was very dependent, died of "pancreatitis" after two years in a sanatorium for questionable pulmonary tuberculosis. During the following year the patient's weight fell from 145 to 115 pounds. Vague lower abdominal cramps appeared. She became nervous, and developed palpitation, weakness and fatigue. Four months before admission she suffered a severe episode of diarrhea lasting eight weeks, and had as many as ten to fifteen bowel movements for a twenty-four-hour period. There was no blood or mucus. The diarrhea slowly subsided, but there had been no menses since its onset.

Physical examination showed an extremely thin young woman. A Grade II blowing systolic murmur was heard over the precordium, loudest at the apex and second left interspace. A few moist rales were present at both bases. The abdomen was flat, with a right paramedian scar, which was slightly tender. There was a moderate white mucoid vaginal discharge and tenderness in the posterior cul-de-sac. There was +++ pitting edema of the left leg, and slight pitting edema of the right.

The blood pressure was 115 systolic, 80 diastolic.

The white-cell count was 10,750, with a normal differential. The hemoglobin was 14 gm per 100 cc. The urine was normal. The stools were repeatedly guaiac negative. A tuberculin test of 1:10,000 was negative. The sedimentation rate was 0.8 mm per minute. The fasting blood sugar was 100 mg, and the total protein 4.5 gm per 100 cc. The prothrombin time was 23 seconds (control, 18 seconds). The sodium was 145.2 milliequiv and the chloride 100 milliequiv per liter, the calcium 9.6 mg, the phosphorus 5.0 mg, and the nonprotein nitrogen eighteen to forty-three mg per 100 cc.

A sigmoidoscopy was normal. A barium enema was negative, the terminal ileum did not fill. A barium meal showed a normal esophagus and stomach. In the distal portion of the jejunum or proximal ileum there was a delay in the passage of barium, and in this portion there were segments of markedly narrowed bowel in which the mucosal pattern was lost. Throughout the remaining ileum, including the terminal ileum, there were multiple similar areas.

During the first month of hospitalization she was essentially afebrile, and on a low roughage and high vitamin, calorie and protein diet she was comfortable except for abdominal distention.

A Miller-Abbott tube passed into the small bowel produced some relief. An ileotransverse colostomy without bowel resection was performed.

An x-ray film on the sixth postoperative day showed an area of increased density in the left lower chest, and a bilateral superficial-femoral-vein ligation was done under local anesthesia. No clots were found. After one month the patient was gradually weaned from intravenous feedings to a low roughage diet. Slight abdominal distention, cramps and occasional slight diarrhea appeared. She was discharged two and a half months after admission.

Second admission (eight months later) In the interval the patient had severe crampy diarrhea in bouts lasting two or three weeks, often watery but never bloody. She was admitted to the hospital for further study. The serum albumin was 3.76, and the globulin 1.41 gm per 100 cc. There was no change in the x-ray findings, and she was discharged after a week in the hospital.

Third admission (fifteen months later) The patient had remained in fair health, had gained about 25 pounds and had married. She had intermittent

attacks of mild diarrhea (with a slight spot of blood on three occasions), but had periods lasting up to a month when she was entirely normal, with regular bowel movements. There was no abdominal pain. Her menses were now normal, occurring every thirty days and lasting four days. Her ankles and legs had been persistently swollen for a year, more severe toward the latter part of the day. The white-cell count, hemoglobin and urine were normal. A small-bowel series showed extensive areas of narrowing throughout the small bowel, the highest one beginning about 18 cm from the ligament of Treitz. She was discharged after four days.

Fourth admission (fourteen months later). She was comfortable without change in her clinical picture until four months before admission, when she tried to manage a six-room house with stairs, and became fatigued. She noticed that the swelling of her legs increased to involve her thighs, hips and abdomen. Dyspnea on slight exertion, palpitation, sweating, and extreme fatigue appeared. Two months before admission a single dose of a mercurial diuretic resulted in a sudden diuresis of 35 pounds of fluid in two or three days.

On examination superficial edema was present below the ninth thoracic vertebra. There was ascites and ++++ edema of both legs.

The blood pressure was 132 systolic, 84 diastolic. The pulse was 96, and the respirations 18.

The white-cell count was 4500, with a normal differential. The urine was normal. The stools gave a + to ++ guaiac reaction. The serum albumin was 3.13, and the globulin 1.72 gm per 100 cc. The alkaline phosphatase was consistently elevated above 10 units, the highest reading was 15.5 units. The cholesterol was 162 mg, vitamin A 1.1 units, and carotenoids 0.4 units per 100 cc. An oral glucose-tolerance test and a vitamin A test were normal.

She was afebrile, and under low salt and mercurial diuretics the edema subsided readily. She was discharged two weeks later on a high calorie, high protein, high vitamin, low salt diet.

Final admission (one month later). For the first week after discharge she felt well, and had no significant accumulation of fluid. In the subsequent three weeks edema fluid increased unrelentingly in spite of vigorous mercurial therapy. In addition one barbiturate capsule nightly was prescribed by her physician.

There was marked edema in the lower half of her body, and ascites was present. The blood pressure was 110 systolic, 70 diastolic.

The white-cell count was normal. The hemoglobin was 10 gm per 100 cc. The urine was normal. Admission stools were guaiac negative, and neutral fats and urobilinogen were normal. Combined fats were markedly increased. The serum alkaline phosphatase was 19.3 units, the serum

albumin 2.62 gm, and the globulin 1.86 gm per 100 cc. A cephalin-flocculation test was negative in forty-eight hours. The van den Bergh reaction was 0.2 to 0.6 mg per 100 cc. The prothrombin time was 19 seconds (control, 16 seconds), the bromsulfalein test demonstrated 25 per cent retention of the dye in one hour. The fluid obtained on abdominal paracentesis was cloudy and yellow, with a specific gravity of 1.009, and contained 90 white cells and 2 red cells per cubic millimeter, a culture was sterile. The liver edge was palpable one fingerbreadth below the costal margin.

X-ray examination of the esophagus showed no varices. On mercurial diuretics and intravenous therapy, including albumin, the serum proteins were restored. The albumin was 4.49 gm, and the globulin 1.59 gm per 100 cc. The edema persisted however.

The patient, always emotionally unstable, became depressed and during the fourth hospital month gradually became drowsy and unresponsive. A Chvostek sign appeared, but disappeared after intravenous calcium therapy. The coma persisted. She died five and a half months after admission.

DIFFERENTIAL DIAGNOSIS

DR. ROBERT R. LINTON. This patient had a number of admissions to the hospital. On the first admission she complained of amenorrhea for four months and swelling of the left leg for nine years. The complaint that she entered with does not strike me as being her chief trouble. I think that becomes more obvious as one reads more of the record. I would like to point out the statement, "four months before admission she suffered severe episodes of diarrhea lasting eight weeks." That is of extreme significance in relation to the remainder of the hospital course and, in fact, to the rest of her life. I am a little disturbed and completely puzzled by the death of her sister from pancreatitis when she was in a sanatorium with pulmonary tuberculosis. I have never associated pancreatitis with pulmonary tuberculosis, perhaps they do occur together.

When I read the record of this first admission I thought, of course, that this patient must have one of two things: regional ileitis or ulcerative colitis, because of the history of severe diarrhea. I will admit that one should not base one's diagnosis entirely on the history of diarrhea lasting for that length of time, but in view of it, I certainly was interested in these two parts of her gastrointestinal tract, the small bowel and the large bowel.

A barium enema revealed marked abnormality in the mid-small bowel down to the cecum, of sufficient severity to produce obstruction of the small bowel so that it was necessary to short-circuit the diseased segment by an ileotransverse colostomy.

A chest x-ray film was taken, and a diagnosis, presumably of pulmonary infarction, was made. Interruption of the femoral vein was carried out.

The fact that no clots were found is of no significance. I personally think if a patient is kept under observation long enough for clots in the common femoral vein to be found, it is comparable to a case of acute appendicitis in which one waits for the appendix to rupture before operating on it.

This case represents a chronic illness involving the intestinal tract. I believe I would leave out the stomach. We have very good evidence—clinically, by x-ray study and by direct inspection of the colon—that it was not involved, and that the disease was localized in the small intestine. It seems to me that this patient had been presented to me to discuss as a reminder of a patient that I had with a similar condition. Unfortunately, I did many more operations on my patient than this patient had, and despite them the disease progressed until the entire small intestine was involved. I do not believe that her amenorrhea had anything to do with the present condition. I think that it was probably secondary to her long-standing debilitating disease. This view is substantiated, I think, because the menses returned after her condition had improved following the ileotransverse colostomy. The edema of her leg, I believe, could have been secondary to an old thrombophlebitis of the lower extremities, which she apparently developed in the left leg at least. The swelling undoubtedly became more marked later on because of the low serum protein. We do not know too much about why people's legs swell, but I am sure that, if there had been obstruction of the lymphatics, the swelling would have been more marked. The left leg swelled, but the right one did not to begin with. I believe that both legs swelled after the femoral veins were interrupted because of the thrombophlebitis, which presumably developed following the ileotransverse colostomy.

It seems to me that this patient's condition is typical of regional ileitis. There are other conditions that one might consider, but I have to rule them out, simply because of ignorance regarding their clinical course. One is tuberculosis of the intestinal tract. I cannot see how it fits into the picture, although it is a possibility. Another is lymphoma of the small bowel. Again, I do not have sufficient evidence on which to base such a diagnosis.

I would like to see the x-ray films before going any farther.

DR STANLEY M WYMAN: These are a few of the films taken when she first came in. They show a normal chest. The esophagus, stomach and duodenum are not remarkable, and the colon reveals no evidence of intrinsic disease. These are films of the small bowel taken over a three-year period, and they show the abnormal areas of small bowel, this being the terminal ileum, entering the cecum, and this being a loop of proximal jejunum. There are multiple areas of abnormal narrowing, with intervening, grossly dilated segments of bowel. The

mucosal pattern is markedly thickened and grossly abnormal.

DR LINTON: These x-ray findings, I think, bear out the written report, and I do not see how one can make any other diagnosis than regional ileitis, with massive involvement of the small intestine.

There are certain chemical studies that are of interest, some of which I am totally unable to decipher. The alkaline phosphatase, the vitamin A and the carotenoids do not help me much in making the diagnosis. To me, they represent abnormalities in bodily function secondary to long-standing illness. The most striking one, and the one that appears to me most significant, is the drop in serum protein, I suppose owing to the chronic condition. Although it was possible to bring this serum protein up to normal level temporarily, it was impossible to keep it there. Another interesting thing is the Chvostek sign, which is merely mentioned here, I believe that it appears in chronically ill patients with regional ileitis. The exact physiology involved, I am not sure about, but I have seen it in patients who had a large part of the small bowel removed. It apparently develops because of the inability to absorb calcium.

In conclusion, I believe that this patient had regional ileitis. She had a disease that we know very little about. If that is what it was, whether treated medically or surgically, the results are not encouraging. From my experiences, I would say that if one does an ileotransverse colostomy to short-circuit the diseased bowel distal to the uppermost lesions of small bowel, the chances of relieving the patient are slim, and the chances of curing her are nil.

DR J H MEANS: I saw this patient twice, in 1945 and again in 1949. We thought the early condition was regional ileitis and the leg condition a postphlebitic one, if I may use the term. Dr Linton saw this patient in 1945. I consulted him and asked if it was subclinical elephantiasis, so called, with postoperative phlebitis, some years before, following appendectomy. I thought the obstruction was lymphatic or venous, or perhaps both. I saw her in the wards when she had swelling in both legs and marked hypoproteinemia, which we supposed was due to lack of small bowel. When I went off service, she was developing a psychosis, and she was transferred to the psychiatric service, where she died. That is all I know. Dr Culver studied her case. Let us call on him.

DR P J CULVER: I followed her for two years. When we first saw her she was in good health, in spite of x-ray evidence of widespread disease. Comments were made at the gastrointestinal rounds on how well she was doing. Then she had this dramatic change. She developed ascites of enormous proportion. It was impossible to explain why she had fluid retention from the diaphragm down and nothing up above. There was wasting of the shoulder girdle, arms and face. The edema and ascites did

not respond to mercurial diuretics. A review of her serum protein levels for the preceding two years made it impossible to attribute the ascites to hypoproteinemia, particularly since there had always been a low serum albumin. When we raised the albumin level with intravenous human albumin, we got a high serum level, but it did not relieve the ascites. Because we could not transfer the edema to the upper half of her body when the foot of her bed was elevated on shock blocks we thought that there must be a block in the inferior vena cava to explain what was going on. We called on Dr. Welch for an opinion, but he did not think caval obstruction was the cause of the ascites.

The liver chemical tests were of interest. She had a normal alkaline phosphatase initially, and it became elevated rapidly, enough to suggest an obstructive element in the liver. The remainder of the liver-function tests, with the exception of the bromsulfalein, were normal, indicating something obstructing the excretory mechanism in the liver. This is as far as we could go toward incriminating the liver. As for the hypocalcemia and its clinical manifestation, tetany, this was probably explainable on the basis that most of these people with regional enteritis have a terrific loss of insoluble calcium salts in the stool. An amazing fact was that, in spite of a damaged bowel, she absorbed vitamin A fairly well. Usually, we see a lowered absorption in this disease. The hypoproteinemia was due to the fact that she had lost so much albumin into the ascitic fluid, and into the edematous fluid, in addition to the fact, as Dr. Means has said, that she did not have enough small bowel to carry on.

DR. CLAUDE E. WELCH: The question put up to me was whether the old thrombophlebitis could have progressed to the point where the inferior vena cava was completely obliterated and extended to the level of the liver, producing, perhaps, a Chiari syndrome and ascites, although it seems unlikely that that would be the cause. The patient had normal renal function, and the renal veins were functioning well. We considered further diagnostic measures in the way of venous catheterization, but she was so sick that we decided not to carry them out.

DR. LINTON: May I read the operating note at this stage? It is as follows:

The small bowel was explored from the ligament of Treitz to the cecum. It was in no place adherent. Many typical lesions of chronic regional enteritis were present, interspersed between short segments of normal bowel. There was only one portion of the bowel that had an area longer than 10 cm. not involved in disease, and that was near the terminal ileum about 35 cm. above the cecum, where there was 30 cm. free of disease.

The extent of the disease found raises the question whether an ileotransverse colostomy was the best treatment for the extensive disease in the patient.

DR. CULVER: It was an emergency procedure because of obstruction. The surgeon's hand was forced. It was not an elective procedure.

DR. TRACY B. MALLORY: A small piece of information was left out of the record inadvertently. At one time when the medical service began to consider the possibility of liver disease, a liver biopsy was done and showed chronic passive congestion of severe degree.

DR. LINTON: I had mentioned that the liver-function tests had nothing much to do with her clinical symptoms, except that the liver was suffering as well as the rest, and I explained the increased bromsulfalein retention on that basis, rather than on that of primary liver disease.

DR. MALLORY: We have had a certain number of patients with ulcerative colitis and regional enteritis who, in the course of years, developed markedly fatty livers and, in some cases, definitely cirrhotic livers. That possibility was seriously considered here, but was apparently ruled out by biopsy.

CLINICAL DIAGNOSES

Inanition, with edema.
Regional enteritis
Ascites of unknown cause

DR. LINTON'S DIAGNOSES

Regional enteritis
Bilateral venous thrombosis of lower extremities
Hypoproteinemia

ANATOMICAL DIAGNOSES

Regional ileitis
Hepatic-vein and vena-cava thrombosis (Chiari's syndrome)
Central necrosis of liver, severe
Ascites
Edema of lower extremities, severe
Multiple pulmonary emboli, microscopic
Operative wounds: ileotransverse colostomy and ligation of superficial femoral veins

PATHOLOGICAL DISCUSSION

DR. MALLORY: Post-mortem examination disclosed very severe regional ileitis. There were innumerable areas of involvement of the small bowel, some of them as short as 1 cm. in length and some as long as 10 cm. The highest one, as the x-ray report stated, was only 30 cm. beyond the ligament of Treitz, and the lowest one extended down to the ileocecal valve, so that the patient had really very little intestine except a duodenum and 30 cm. of jejunum that could be considered normal. We did find a thrombus in the inferior vena cava, which was about 10 cm. in length. It started above the level of the renal veins, which were entirely uninvolved, and extended up above the mouth of the hepatic vein and then there was retrograde thrombosis of the hepatic veins throughout the liver, even down to the very small ones, making a characteristic picture of so-called Chiari's syndrome. This was quite consistent with the liver biopsy. The finding of chronic passive con-

gestion of the liver in the absence of heart disease suggests obstruction between the level of the hepatic vein and the right auricle at some point. The liver itself showed rather extensive secondary degeneration, part of it looking simply like extremely marked chronic passive congestion and part of it being a picture of incomplete infarction. The age of the intrahepatic thrombi was variable. Some of them seemed quite fresh, and others showed marked organization and must have been present weeks — and perhaps months or more.

DR CULVER: Do you think this could explain the ascites that had been present for six months?

DR MALLORY: It is hard to estimate the age of these thrombi with exactness. An otherwise healthy person will organize a thrombus comparatively rapidly, a very ill patient may require two or three times as long to effect the same amount of organization. It is quite possible that these thrombi are of longer duration than one would estimate from ordinary criteria.

DR CULVER: Is not the amount of ascites in the case unusual for regional ileitis? In fact, I have not seen a case with more than minimal fluid in the abdomen. Could the ascites be explained by blockage of the lymphatics with an infiltrative reaction throughout the small bowel rather than any other cause, such as liver disease, portal hypertension or hypoalbuminemia?

DR MALLORY: I had not thought of that possibility but did not see any striking evidence of lymphatic dilatation in the bowel, and I would be more inclined to think it was due to portal hypertension.

DR LINTON: The vena cava was not completely occluded?

DR MALLORY: No, perhaps only one third.

DR WELCH: Do you think this was the end result of ascending thrombosis of the vena cava, or possibly that the thrombosis in the liver was more or less simultaneous? The thrombi met in the middle, which is a peculiar picture.

DR MALLORY: It is possible, I cannot say with certainty whether the thrombus started in the hepatic vein or in the vena cava.

DR LINTON: Perhaps it was started by the biopsy.

DR MALLORY: It is frequently recorded in cases of Chian's syndrome that there is thrombosis both in the vena cava and in the hepatic vein.

lateral side of the right thorax, from the level of the sixth rib down into the flanks and around to the back. It occasionally radiated to the region of the anterosuperior iliac spine, but never to the left side, shoulder, scapula or umbilicus. It was steady and sustained, never colicky. The pain was not related to meals. There was no headache or urinary symptoms. His appetite had diminished. The pain subsided after two weeks, but a residual soreness persisted. Attacks recurred about once each month, lasting one or two weeks. The pain was so disabling that he was unable to work and was virtually an invalid. There was no weight loss. The more recent seizure started two weeks before admission.

He had scarlet fever at six years of age, but no cardiac or renal sequelae were recalled. At the age of twelve, he had rheumatic fever, and was confined to bed at home for one year. There were several recurrences until fifteen years of age. Four years before admission he entered another hospital with pneumonia. For many years, he had been aware of vigorous heart action, especially at night, when he was disturbed by the shaking of the bed with each heart beat. He was able to climb one flight of stairs rapidly without feeling excessively breathless. He slept lying flat. There was no ankle edema.

Physical examination showed a pale, asthenic, well nourished man. The heart was markedly enlarged, the apical impulse being prominent and visible in the seventh interspace in the axillary line. Rough and blowing systolic and diastolic murmurs were loudest at the aortic area, and radiated to the neck and the apex. The second pulmonic sound was faint. The rhythm was regular. The lungs were clear and resonant throughout.

On abdominal examination two points of deep tenderness were found in the anterior right flank about two fingerbreadths below the costal margin extending posteriorly for an area about 15 cm in diameter, and in the right lower quadrant just above Poupart's ligament.

The blood pressure was 180 systolic, 30 diastolic.

The white-cell count was 10,200, and the red-cell count 5,300,000. The urine had a specific gravity of 1.012 and gave a +++ test for albumin, the sediment contained occasional white cells and hyaline and granular casts. A culture was negative, and a concentration test reached up to 1.015. The nonprotein nitrogen was 33 mg per 100 cc. The phenolsulfonephthalein test showed 15 per cent excretion in fifteen minutes, and 50 per cent within the first hour. An electrocardiogram was abnormal, suggesting left ventricular strain. The QRS complex was slurred and widened to 0.10 second. There was slight left-axis deviation, with sagging ST segments and inverted T wave in Lead 1 and diphasic T wave in Lead 2, the PR interval was 0.20 second.

CASE 35242

PRESENTATION OF CASE

First admission. A twenty-seven-year-old photographer entered the Out-Patient Department complaining of recurrent attacks of right-flank pain.

Five years before admission, he had an attack of right-sided pain that was very severe and forced him to go to bed. The pain was situated on the

A chest x-ray film showed clear lung fields and a markedly enlarged heart, chiefly in the region of the left ventricle. There was a small amount of fluid in both costophrenic angles.

Intravenous pyelography showed no definite filling of the kidney, pelves or ureters. Some dye was seen in the bladder after twenty minutes. On retrograde pyelogram and cystoscopy only the right meatal orifice was found. Retrograde filling on this side showed a short ureter, but the renal pelvis was superimposed on the mid-sacrum.

Under observation as an outpatient, acute episodes of pain recurred, and eleven months after his first examination he was admitted to the hospital. The previous findings were confirmed, but since his pain diminished in intensity he was discharged eight days later to return at the onset of another attack for a diagnostic novocain block. Another retrograde pyelogram confirmed the previous finding of a single pelvic kidney. The calyces appeared small but were otherwise normal.

Second admission (eight months later) The patient returned because of an acute attack. Right paravertebral novocain injection was employed, and the pain was relieved temporarily.

Third admission (one year later) A right lumbo-dorsal sympathectomy was done, with immediate relief of pain.

Fourth admission (two years later) The patient complained of severe pain, localized to an area 15 cm in diameter just to the right of the spine and below the scapula, requiring demerol or morphine for adequate relief. In addition, in the two years after operation dyspnea on exertion had increased, and on repeated occasions he was awakened by a smothering sensation, which forced him to sit up-right and go to an open window. The heart was increased in size over previous examinations, and loud harsh systolic and diastolic murmurs were heard at the base. Slight presystolic accentuation at the apex and a mid-diastolic rumble were noted. A normal sinus rhythm (rate of 90) was present. The blood pressure was 190 systolic, 50 diastolic.

The sedimentation rate was increased to 11 mm per minute. Moderate numbers of *Staphylococcus albus* and a few colon bacilli were cultured from the urine. The nonprotein nitrogen was 48 mg per 100 cc, and the blood chloride was 111 milliequiv per liter. An electrocardiogram showed a PR interval of 0.20 second and prominent S wave in Lead 2, the T waves were inverted in Lead 1, diphasic in Lead 2 and upright in Lead 3. Sweating and skin-temperature tests demonstrated complete sympathetic regeneration. A Graham test was negative. Therapy included digitalization, a large fluid intake and demerol for pain.

After two months the patient was transferred to another hospital for chronic convalescent care, and remained there for four months.

Fifth admission (seven months later) The patient was readmitted complaining of recurrent pain in the right posterior thorax. The physical findings included marked pallor and forceful arterial pulsations in the neck. The heart was markedly enlarged, the point of maximal impulse being at the anterior axillary line in the seventh interspace, a protodiastolic gallop was present at the apex. The following murmurs were found: a Grade III, rough, aortic systolic murmur, a Grade III, long diastolic blow at the base, left sternal border, apex and axilla and a Grade II, rather high-pitched apical systolic and an apical diastolic rumble. The lungs were clear. The liver edge was palpable at the costal margin, with tenderness. There was slight ankle edema.

The blood pressure was 230 systolic, 0 diastolic.

The sedimentation rate was 58 mm in sixty minutes. The red-cell count was 4,280,000, with a hemoglobin of 9.5 gm per 100 cc. The nonprotein nitrogen was 78 to 125 mg per 100 cc. The chloride was 109 milliequiv, and the carbon dioxide 16.6 milliequiv per liter, and the creatinine ± 2 to ± 9 mg, the calcium 7.5 mg, and the phosphorus 5.5 mg per 100 cc.

Final admission (three years later) The complaint at this time was during the interval in which the patient was seen frequently as an outpatient and inpatient. His complaints were right-chest pain (relieved only by sedation), dyspnea and ankle edema, and repeated severe epistaxes requiring packing and blood transfusions. On examination bilateral moist rales were heard at both bases, more marked on the right, with slight dullness on the right. Right-upper-quadrant tenderness in the abdomen was noted. There was a +++ pitting edema behind the malleoli. The blood pressure was 240 systolic, 40 diastolic.

The white-cell count was 21,100, and the hemoglobin 7.2 gm. The specific gravity of the urine was 1.010, with a +++ test for albumin and a + test for sugar. Many white cells and amorphous granular material were present in the sediment. The nonprotein nitrogen was 200 mg, the fasting blood sugar 105 mg, and the total protein 6.1 gm per 100 cc, and the carbon dioxide 10.5 milliequiv, the sodium 124.5 milliequiv, and the chloride 90 milliequiv per liter.

The patient developed progressive respiratory distress, with increasing moist rales in both lungs. He died on the seventh hospital day.

DIFFERENTIAL DIAGNOSIS

DR HOWARD B. SPRAGUE Those who took care of this patient had the opportunity of watching him for seven years. I have had less than one day to consider this situation. I hope they were happier about it than I am. It does seem, however, that there is enough in the history to explain why the patient died, but I am not sure what caused his

prolonged disability — namely, this peculiar kind of pain

To begin with, he began to have trouble when he was twenty-two years old, and he had for about half the time in the next seven years recurring right-flank pain, which lasted one or two weeks at a time and came on about once a month. That leaves him not much free time without pain. I assume from this history that he had rheumatic heart disease with aortic involvement — aortic regurgitation and some degree of aortic stenosis. There was a questionable mitral diastolic rumble, which could have been an Austin-Flint murmur, but on a statistical basis I suppose we would say that there was both mitral and aortic involvement. There was apparently congenital absence of the left kidney and a solitary pelvic kidney on the right side with a short ureter, which would indicate that it was a developmental affair. There was normal rhythm in the heart — that is, no auricular fibrillation, and predominantly an aortic lesion. This does not influence us toward the thought of multiple embolic phenomena. Certainly a patient cannot have emboli every two or three weeks for seven years, I would think, without having more to show for it. The pain was relieved by both the paravertebral block and the right lumbodorsal sympathectomy. Dr. J. C. White is here and will presumably tell us about this later. But since nothing is said in the history about whether anything peculiar was seen when the operation was performed, I shall assume that probably nothing was seen. He had progressive anemia, progressive renal failure, uremia and a questionable urinary infection. The epistaxis was presumably on the basis of hypertension and renal state, although one has to think of active rheumatic fever and nosebleeds.

Let us consider this pain, which had a distribution as high up as the sixth rib in the back but which seems mostly to have been right-flank pain and below the costal margin, at times to the crest of the ilium. It seems to have been more below the ribs than up in the chest, and there is nothing in the x-ray report to suggest anything wrong in the chest. There does not seem to have been anything on which to base a suspicion of gall-bladder or liver difficulty. Of course, acute recurrent liver congestion that occurs in mitral stenosis has to be thought of too, but this does not quite seem like that. He did not have a large tender liver related to the attack. The Graham test was negative. The distribution of this pain would seem to me to be renal in its position, and I am interested to know, since he had only one kidney and it was down in the pelvis, whether he maintained the ordinary renal distribution of pain, if he had trouble with that kidney.

Perhaps Dr. White would be willing to answer that for

Dr. J. C. White. I would expect he had, because it would drag the nerve supply with it. When I was working in the Anatomical Laboratory of Professor Hovelacque in Paris, I dissected a cadaver with a very similar pelvic kidney, which derived its blood supply from the common iliac artery. The nerve supply came down from above in the usual fashion.

Dr. Sprague. That was the way I had argued — perhaps the nerve supply would be more likely to maintain its normal relation with the kidney than the blood supply. If we think in terms of development of the kidney in that area, and its failure to "ascend," it was actually being dragged down by the short ureter, which did not allow its blood supply to develop normally. I see nothing in the history to suggest urinary obstruction — at least there was nothing resembling a Dietl crisis, and a biologic study would not indicate dilatation of the kidney. I have been informed that the x-ray films are not available at the present time, but that is the way that I interpret it from the history. So I am going to say, in spite of congenital anomaly of the kidney, that there was rheumatic rather than congenital heart disease, with aortic and perhaps mitral involvement, and that there was a progressive change in this solitary developmentally abnormal kidney in the nature of a true nephritis, perhaps of vascular origin with secondary infection. He had uremia and mounting hypertension, and then, to explain the pain, I am forced to fall back on the relation between the heart, aorta and the abnormally placed kidney. I was intrigued to think about a multitude of vascular anomalies commonly occurring in this region to account for this as being vascular pain in some way, probably radiating over an extensive pathway, but it may be that the kidney was so placed in relation to the aorta, and bound down by adhesions, that the severe aortic regurgitation acted in some way to irritate the attendant nerves. I would like to find out what was really wrong with this patient.

Dr. White. The urologists believed that this patient did have an ectopic kidney. That was fairly well proved. We asked them if they would do a retrograde distention of the kidney pelvis and single ureter, but they were reluctant to do so, because it was his only kidney. That would have proved whether the pain of which he was complaining in his paroxysms was of renal origin. Be that as it may, he did not have pain in the flank or groin after operation. When he came in two years later the urologists were willing to pass a ureteral catheter up to the pelvis and distend it, they found that it produced no pain. It was therefore evident that the kidney was denervated and that the pain he was having in the chest was not of renal origin. The operation was similar to that done for hypertension, the twelfth rib being taken out. I removed about 5 or 6 cm. of the major

splanchnic nerve and the sympathetic ganglionated chain from the tenth thoracic to the second lumbar segment, which would be sufficient to denervate the normal kidney. I wonder if Dr. Sprague has any explanation why the patient continued to have right thoracic pain? I have seen one patient with a tense liver capsule from cardiac failure who had pain of this sort, and I have also seen continuous discomfort in patients with active rheumatic heart disease. I remember one such case that Dr. T. Duckett Jones and Dr. Edward F. Bland had at the Good Samaritan Hospital, and they asked me to do a paravertebral injection. The patient had intermittent angina pectoris and steady pain in the right chest. Both types of pain were relieved following alcohol injection of the cardiac nerve.

DR. SPRAGUE: That was probably a mitral case.

DR. WHITE: The patient, a young woman, as I recall her, had aortic regurgitation, but I do not remember whether she had mitral disease as well.

DR. WILLIAM CHAPMAN: As I recall, the first pain in the case under discussion was located between the vertebra and medial border of the scapula and was reproduced by injection of 6 per cent saline solution in the same segment on the other side, which suggested a cerebrospinal or somatic pain. One expected, as Dr. Sprague did, that it was related to the grossly enlarged heart, and it was difficult to see how the enlarged heart could be pressing on the right side.

DR. SPRAGUE: I was trying to get out of my dilemma by saying that by sympathectomy we pushed the pain higher as we push anginal pain to the other side in some sympathectomized patients.

DR. WHITE: Yes, anginal pain may appear on the opposite side, and occasionally it may shift up into the jaw.

DR. SPRAGUE: True, but I was not quite clear about the amount of regrowth in the sympathetics.

DR. WHITE: I think that very often regeneration of peripheral vasomotor fibers, and much more rarely of the visceral nerves, may occur.

CLINICAL DIAGNOSES

Uremia

Chronic nephritis in single congenital ectopic kidney

Rheumatic heart disease

DR. SPRAGUE'S DIAGNOSES

Rheumatic heart disease, aortic regurgitation and stenosis and slight mitral stenosis

Congenital solitary pelvic kidney, with renal pain

Chronic glomerulonephritis and uremia

ANATOMICAL DIAGNOSES

Rheumatic heart disease, aortic stenosis and regurgitation

Adhesive pericarditis, chronic, with calcification

Congenital anomaly—single pelvic kidney

Chronic glomerulonephritis

Hyperplasia of the parathyroid glands

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: I think our autopsy findings were very much like Dr. Sprague's clinical diagnosis. We can explain the cause of death very readily, I am not sure that we can explain the cause of pain. The patient had the largest heart that we have ever seen in this laboratory (it weighed 1500 gm.), and he evidently had three causes for that enlargement. One was a severe rheumatic involvement of the aortic valve, with both regurgitation and stenosis. The mitral valve was essentially normal. He also had an adherent pericarditis, with considerable amounts of calcification in the pericardium. He unquestionably had hypertension on the basis of renal disease.

There was only one kidney, which lay in the pelvis and had a short ureter. The kidney had two arteries, the source of one of which was at the bifurcation of the iliac vessels, but the other smaller artery was not traced to its source. The single kidney weighed only 110 gm. and was scarred and granular, without, however, any dilatation of the pelvis. The microscopical sections showed an old, severe glomerulonephritis, so that there is ample explanation for renal failure. He had moderately enlarged parathyroid glands, as one would expect with such long-standing renal insufficiency. We found no involvement of the mediastinum that we could recognize, and except for the large heart and the adherent pericardium there was nothing in the thoracic cage that would explain the later episodes of pain in the thoracic region.

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are that with increasing knowledge they are making up their minds in favor of free enterprise and voluntary systems of health insurance in which they can determine their own stake. They are willing to go into partnership with their doctors.

The continuing education of the public along these lines has been assumed by the medical profession, which is in the best position to carry on such a course of instruction. Its extension must be in the hands of informed laymen whose interests are obviously those of the public that they represent.

Every physician, nevertheless, as was indicated at the gathering of physicians and representatives of women's auxiliaries held in Boston on May 1, as an unofficial spokesman of his profession. Armed with the material that is directed to him through organized professional channels, he is delivering to his own segment of the public accurate information for further intelligent distribution.

While words must constitute the greater part of the ammunition in this battle for the continuance of an improved American way of life, consistent with liberty and the pursuit of happiness, words are fortunately not often lethal. They have their dangers, however, and too heavy a barrage must not be laid down. The old refrain "It's a terrible death to be talked to death" must still be borne in mind. There is a limit even to the amount of propaganda that one can sustain, and survive.

A WILLING PARTNERSHIP

It is an accepted thesis that the most important consideration in selling the idea of good medical care to the American people is to make them aware of what constitutes such care, and then to deliver it. They must be informed of its limitations as well as its accomplishments. They must know what it is worth in dollars and cents, and why. They must be directed toward the fairest and most economical way of meeting those costs.

From here on, mystery and magic, the ancient cloaks of medical grievance, are out.

Already, thanks to the kind and well intended efforts of various persons and organizations working for the adoption of compulsory health insurance, the people are taking great interest in the quality and distribution of medical care. The indications

EPIDEMIC ENCEPHALITIS IN RETROSPECT

ELSEWHERE in this issue of the *Journal* Ayres and Feemster present a nine-year to ten-year recheck on all the children who survived the 1938 outbreak of eastern equine encephalomyelitis in Massachusetts. The fact that only 1 child out of 34 is known to have come through unscathed is indisputable evidence of the violence of the infection with the virus of this particular disease. Twenty-five of the cases ended fatally, and 7 of the 9 survivors have varying degrees of mental and physical handicaps.

It is fortunate that a virus that causes such a stormy course seldom spreads to man. When it is considered that 70 per cent of human beings and 90 per cent of horses die of the infection with the

eastern virus, compared to only 10 per cent of the human beings and 20 to 30 per cent of the horses with the western virus, it can be understood why large outbreaks can occur in the western part of the country, where the latter is the predominating variety, whereas only a few isolated cases or small outbreaks occur in the eastern areas, where the eastern virus is more frequently found. An etiologic agent that kills off most of the hosts attacked has difficulty in surviving.

The progress report in this issue summarizes present knowledge of the public-health aspects of the six more important viruses that cause epidemic encephalitis. Much additional information is needed to provide a clear understanding of the peculiar geographic localization, not only of the eastern and western viruses but also of the virus of the St. Louis encephalitis. All these diseases can be transmitted by insect vectors prevalent in the eastern United States as well as in the West, but up to the present time most of the outbreaks have occurred west of the Mississippi River.

A state-wide mosquito survey carried on in 1939, as a consequence of the 1938 outbreak, furnished much useful information regarding the varieties and habits of the mosquitoes in Massachusetts. This information will be valuable if another outbreak of eastern equine encephalomyelitis should occur, or if one of the other two viruses should be transported into this area.

—WHO HELP THEMSELVES

THE American Red Cross performed such a variety of heroic services to the country during the war that it is hard to bear in mind the continuing value of some of them in the uneasy days that have succeeded the conflict. Of special importance in this respect is the training in the elements of home nursing that so many women received in those days. This training, less dramatic than first aid, was equally useful, less impressive than automobile repairing, it was more practical.

It should be a source of comfort in innumerable households as well as a contribution to the sense of security of many family physicians to know that

the Home Nursing Courses of the Red Cross are not only continuing but expanding their services.

These courses are divided into two units, one on the care of the sick and one on mother, baby and family care. Each, independent as a unit although complementary to the other, consists of six two-hour lessons. They are taught by qualified graduate nurses. Elementary as they are, they may serve the purpose of turning a willing but ineffective member of the family into one capable of caring for patients who are not critically ill or completely helpless, and for giving adequate attention to mothers and babies. Such service, particularly as it may be augmented by the visiting nurse, can save many hours of expensive hospitalization and in many instances render unnecessary the search, so often fruitless, for a high-priced nurse willing to go into the home. Information regarding the courses may be obtained from any Red Cross chapter.

The paradoxical situation exists today in which the products and the skills of science and industry are virtually beyond the reach of a considerable proportion of householders. Service of any nature has become so dear or so scarce that a return to the days of personal self-reliance is almost inevitable. More and more must the homeowner of today learn through necessity to saw a straight line and to set a pane of glass.

In matters ranging from replacing buttons to patching pants, from putting pans under leaking roofs to conquering the complexities of bed baths, the old adage that God helps those who help themselves is being reaffirmed. The hand-worked sampler may have given way to offset printing, but Home Sweet Home, while still the dearest place on earth, can be made a little less expensive if every member of the family makes some personal contribution.¹

GRIM REAPER

TRAFFIC deaths in the United States, according to The Travelers Insurance Companies, dropped 1 per cent in 1948. The total, in round figures, was 32,200 as compared with 32,500 in 1947. Personal injuries, however, increased 8 per cent to a total of 1,471,000, the 1947 figure having been 1,365,000.

Pedestrians, apparently, can jump faster, even if no farther

More than a third of the deaths and nearly a quarter of the injuries were attributed to excessive speed, and this has been the important factor in recent years. Like Mr Toad of Toad Hall, too many human beings experience changes in personality when under the influence of intoxicating motion. This applies particularly to the more adventurous, less cautious ages between eighteen and twenty-four, which are responsible for more than their share of both deaths and injuries.

It is difficult to know surely whether American automobile manufacturers are creating or supplying a demand when they continue to produce increasingly speedy and increasingly costly motor cars. Every conservative instinct cries out for the opposite policy, but it appears that the majority of democracy's fellow travelers live literally for the moment only.

MASSACHUSETTS MEDICAL SOCIETY

Presidential Address

Your vote of confidence in me is deeply appreciated. No member of the Massachusetts Medical Society receiving this great honor could possibly fail to be duly impressed. I know that there are many among you more deserving of this recognition than I. Having observed the work of the Society closely for many years and pursuing a careful study of its activities during the past twelve months, I realize the tremendous responsibility you have placed upon me. It is with full awareness of my own inadequacies that I accept this position as your moderator. I assure you that I am fully cognizant of the fact that this is no dictatorship — no one-man show. I earnestly beg of you to give the Society your best effort, and to give me your guidance and counsel throughout the coming year. We must work in close co-operation and in harmony, without selfish interests but with a steadfast purpose for the good of the Society as a whole and for the benefit of humanity.

I suppose every president who has preceded me has believed that his specific term of office came at a critical period. Doubtless many have regarded their terms as offering an unparalleled opportunity for the Society to turn its attention to the problems of the moment. Always there have been emergency measures of one kind or another to be dealt with, and always, as now, the constant desire to advance medical education and improve medical care. This attitude, which was the prime motive in the organization of the Society one hundred and sixty-eight years ago, has never changed. There has been steady progress in the past so that we can well take pride in the quality of medical service now available in this state and in this nation. We cannot accept a complacent attitude concerning these matters. The hope is that never in the history of the Massachusetts Medical Society will there be a smug feeling of satisfaction regarding our accomplishments that will in any way detour us from the straight and narrow road in seeking a higher level

The serious national problems before us are demanding our constant attention. Our educational program is going well, and the people of this country are being awakened to their situation. It is apparent that they are eager for knowledge concerning all matters pertaining to their health and to their rights as citizens. Over 600 organizations in the United States have passed resolutions opposing compulsory health insurance. This is encouraging, and the effort expended appears to have been worth while. We must not allow these favorable reports to lull us into inactivity however. We must learn and dispense the true facts with constant vigilance and without interruption. We have the satisfaction of paying for this program ourselves even though we are also paying through taxation, in part, for the propaganda of our clever opponents.

We shall need to marshal our strongest forces on the national battlefield for some time to come. We have, however, reserves that are available for a continuation of our efforts to advance the art and science of medicine. These are and always have been carried out for the prevention of disease, for the improvement of health and for the relief of the sick.

Your many committees set up to study our various problems and to expedite the responsibilities of the Society have been carefully evaluated. Some whose purposes have been accomplished are recommended for discharge. The personnel of new ones endorsed by you tonight will be announced after due thought and consideration.

You have approved of the recommendation of the Committee on Public Health to appoint a subcommittee for the purpose of developing pilot diagnostic clinics. It is my understanding that this is to be done in co-operation with the various specialty groups already working along these lines, and that such clinics are to be staffed by the medical personnel of the district in which they are established and in already existing community hospitals. The beneficial effects already demonstrated by

the Tuberculosis League, the State Cancer Society, the Committee on Diabetes and the Heart Association are well known to you. If the mechanism of clinics for general examinations can be satisfactorily worked out for all concerned, we shall have made a great forward step. It is requested that those of you who are skeptical of such a venture offer constructive criticism and lend your aid to this endeavor.

American medicine has been severely criticized about the inadequacies of medical care. Much has been said regarding the shortage of doctors. We are told that, in certain localities at least, emergency medical service is difficult to obtain, particularly on week ends and holidays as well as at night. We have also had reverberations that are not to our credit regarding the charges made, in some instances, for professional services rendered. This appears to be a proper time to consider seriously these problems and first of all to find out what the true situation is and to see what needs to be done about it. We realize that such complaints are greatly exaggerated and that an isolated instance may make a bad impression for the Society as a whole. On the other hand it is to our best interests to rectify these errors if they exist.

Without any doubt, a nation-wide survey concerning the health needs of people should be made. It is hoped that a commission set up along the lines of the Hoover Commission will be established to carry out such a study. Since it will be necessary for each state to participate in such a program, it seems that we should be in a better position if we considered looking into our own situation now. It would be necessary to have each district participate in this procedure with the eventual co-ordination of the facts. What we can do about inadequacies, if they exist, will be a matter for future consideration.

I have had the privilege during the past year of attending the majority of the meetings held by your various committees. The sacrifice of time and the tedium of travel do not interfere with the seriousness of purpose that these men display. The Society as a whole and the citizens of the state it serves should be duly grateful for such devoted service. Since there are so many committees already, you may not be willing to support me in the request I make for one more. I hope, however, that you will and that we can start our survey of the availability of adequate medical care in the Commonwealth.

In conclusion, I should like to make a strong appeal to the district presidents. It is obvious to all that there are times when it is impossible for a committee man to attend a stated meeting of his committee. It appears, however, that these

absentees are more apt to be representatives of certain of our districts. I am sure that if the district president would study the situation and more carefully make his appointments we should have a better representation. We want the advice and counsel from all areas and urge that every effort be made to make our society truly representative.

Again, I thank you for your confidence in me and once more ask for your help and counsel, and for your charitable and lenient attitude when my procedures fail to meet your full approval.

ARTHUR W ALLEN

CORRESPONDENCE

MAKE HASTE SLOWLY

To the Editor There is no doubt that most doctors are opposed to President Truman's plan of health insurance. But how many of them failed to vote against the politicians who have undertaken the transformation of our republic into a socialized democracy is of pertinent interest.

As members of a learned profession, we should naturally embrace the conservative. Whatever socialistic changes we may happen to favor we should prefer to have come gradually. We certainly can hardly approve of the rate at which stark socialism has been growing in this country. We are well aware of the waste and inefficiency of the divers mushrooming bureaus, which tend to destroy our individuality and to weaken our souls.

In our next political campaign, may it not be more discreet for us to resist socialism in general as individuals rather than as a group exposing our profession to the charge of selfishness and trade-unionism?

G W HAIGH, M D

Worcester, Massachusetts

NOTICES

ANNOUNCEMENT

Dr Donald T Chamberlin announces the removal of his office from 422 Beacon Street, Boston, to 1180 Beacon Street, Brookline.

SOUTH END MEDICAL CLUB

A luncheon meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, June 21, at 12 noon. Dr John G Downing will speak on the subject "Local Therapy in Dermatology."

Physicians are cordially invited to attend.

94TH INFANTRY DIVISION LECTURES

The 94th (Bay State) Infantry Division is sponsoring a series of monthly lectures by prominent physicians in their respective specialties. The fifth lecture will be held in the auditorium of Boston University School of Medicine, 80 East Concord Street, Boston, on Tuesday, June 28, at 8 00 p m. Dr Henry M Lemon, Captain, Medical Corps Reserve, will speak on the subject "Recent Advances in the Diagnosis of Malignant Disease."

All interested physicians, whether reserve officers or not, are cordially invited to attend this carefully planned program. Reserve officers will be given one point credit. Excellent films will also be shown during this period.

(Notices concluded on page xi)

JUNE 23 1949

BOSTON

Six cases of TEF (1 in a stillborn infant) among 30,497 live births were found in the records of the Boston Lying-in Hospital for the years 1934 to 1945, inclusive. On this basis the frequency of TEF, in the Boston area, may be estimated as at least 0.2 per 1000 live births, the major variable prob-

ably being the missed case—the stillbirth and asphyxial death in which no autopsy was performed

All observers are agreed that esophageal atresia is a rare condition. Murphy⁵ found 13 cases recorded on death certificates in Philadelphia during a five-year period when 166,451 live births occurred—not quite 1 per 10,000 live births

Case Mortality

Before surgical methods were applied to the treatment of TEF, survival was a rare accident dependent on the existence of a defect so small as to be of no critical consequence. Plass² assembled data relative to the length of life of 120 babies with the anomaly as shown graphically in Figure 1. Five were still-

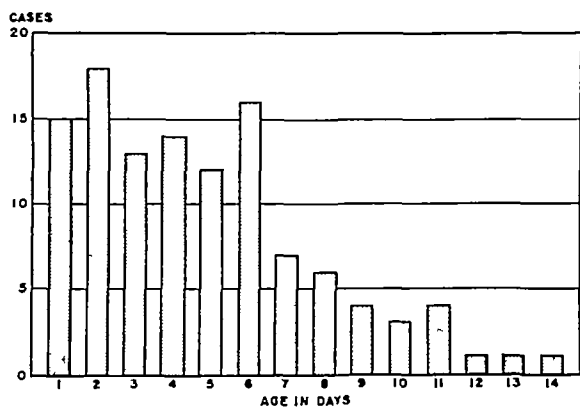


FIGURE 1 Age at Death of 115 Babies with Tracheoesophageal Fistula (Based on Data of Plass²)

born. Mean survival time for the other 115 may be calculated as 4.8 (± 3.5) days.

Swenson⁶ reports that with modern surgery 57 of 113 patients operated upon in the last eight years at the Children's Hospital, Boston, have survived, and only 5 postoperative deaths have occurred in the last 32 patients.

Familial Occurrence

None of the families of the 107 infants in this series was known to include another member with esophageal atresia or TEF either in the same or in a preceding generation.

Among the histories of 136 babies with esophageal atresia Plass² found none with multiple familial occurrences, but Lanman,⁷ in 1940, reported the condition in a brother and sister, born one year apart. No case of the anomaly recurring as a familial trait in successive generations has been encountered in a comprehensive review of the literature on the subject.

Sex Incidence

There were 62 male infants and 45 females in this series. Added to 25 males and 19 females in

two previously reported series,^{2, 4} a ratio of 87 (57.6 per cent) males to 64 females is obtained. Normal expectancy for Massachusetts, 1939 to 1943, inclusive,⁸ is 52.6 per cent males; the difference is not significant.

Birth Weights

Birth weights recorded for 87 infants with TEF were significantly lower than those of 1000 babies of a general lying-in-hospital population, as shown in Figure 2. The birth weight of 18 of these infants whose mothers had hydramnios averaged 5 pounds, 2 ounces, that of the remaining 69 averaging 6 pounds, 1 ounce.

Relation to Maternal Factors

Age. The ages of 75 mothers who gave birth to a baby with TEF are compared with those of mothers in Massachusetts during the years 1939 to 1943, inclusive (Table 1). The disease appeared more frequently than was to be expected by chance among the progeny of older women, though this trend is far less striking than that for mongolism.⁹

Maternal marital status. Four of 102 mothers (39.2/1000) were unmarried (a fifth, though married, had the baby illegitimately), normal expectancy for the general white population, United States Registration Area, 1939 to 1944, inclusive,⁸ being 18.4/1000.

Previous miscarriages and stillbirths. The birth of 19 of 79 infants with TEF had been preceded by a miscarriage or stillbirth, 12 by one, 4 by two, and 3 by six such pregnancies. The 79 mothers had a total of 277 conceptions, of which 32 (11.6 per cent) ended in spontaneous abortion, as compared with an incidence of 10.6 per cent in 1150 pregnancies over a six-year period studied by Hertig and Livingstone¹⁰ in a private practice at the Boston Lying-in Hospital.

Birth order of the affected child. In 76 records 30.3 per cent of the mothers were found to be primiparas. According to Gates¹¹ 41.2 per cent of children in Canada are expectedly first-born. Expectancy for this series computed by the Greenwood-Yule rule¹² is given in Table 2. As in mongolism¹³ the risk was found to be greater with each successive pregnancy.

Maternal health. Among 87 case records evidence of chronic maternal disease during pregnancy was encountered 12 times. Hyperemesis gravidarum was noted 3 times, 3 mothers had goiter, 3 had pre-eclampsia, and 3 others had pelvic deformities, 2 had chronic pyelitis, and 1 had tuberculosis with effusion and pneumothorax. The significance of such findings is problematic. Acute illnesses and ante-partum hemorrhages that could be localized in time tended to occur in early pregnancy as shown in Table 3 and 4.

Unusual placental environment. The clinical observation of earlier writers^{2, 14} that a significant

association exists between TEF and maternal hydramnios was confirmed by finding of the condition 20 times among 87 mothers. In addition, abnormalities of the placenta (Table 4) were encountered

anomaly (of the heart). During the tenth pregnancy the mother developed hydramnios, and at term the baby was found to have TEF. A subsequent pregnancy resulted in a living child, a twelfth in a miscarriage in the 6th month, and a thirteenth in a living child.

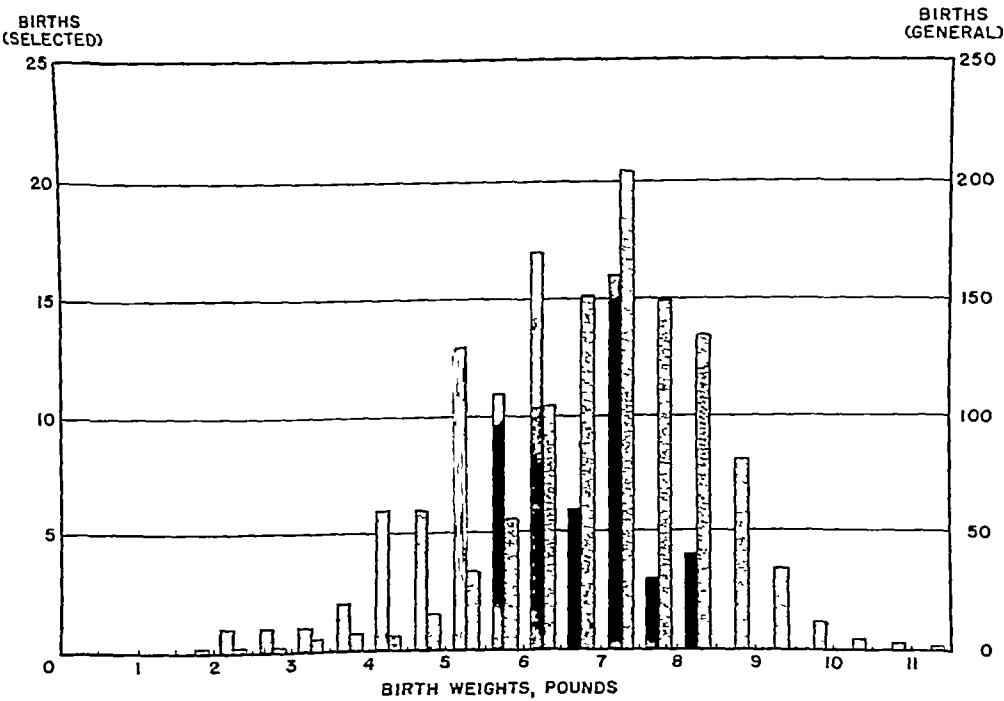


FIGURE 2 Distribution of Birth Weights of 1000 Living Babies of a General (Lying-In) Hospital Population (Stippled Bars) and 87 Living Babies with Tracheoesophageal Fistula (Shaded Bars)

frequently enough to suggest that particular search for similar associations should be made in the future. Four pairs of twins as the product of 107 births

CASE 2. A 20-year-old primipara gave birth to twins after a pregnancy complicated by hydramnios. Excess fluid was observed in the amniotic sac of 1 infant with TEF (who also exhibited mongoloid features) but not in that of its normal fellow.

CASE 3. A 31-year-old woman had had a miscarriage, and irregular periods prior to conception of the baby with

TABLE 1 Maternal Age and Esophageal Atresia *

MATERNAL AGE	BIRTHS	
	INFANTS WITH ESOPHAGEAL ATRESIA	GENERAL POPULATION MASSACHUSETTS (1939-1943)
15-19	0	18 911
20-24	16	99 185
25-29	20	114 040
30-34	19	73 094
35-39	14	37 611
40-44	0	9 909
45-49	1	650

* Among 75 mothers of infants with TEF the mean age was 29.17 yr (standard deviation 6.25). Among 353 400 mothers in the general population the mean age was 28.18 yr (standard deviation 5.85). The difference of the means was 0.99 and the standard deviation of the difference 0.229. The critical ratio was 4.3.

TABLE 2 Birth Order among 76 Infants with Tracheoesophageal Fistula

BIRTH ORDER NO	OBSERVED	EXPECTED %	EXPECTED CT
1	23	41.75	55
2	26	18.75	159
3	9	5.75	152
4	5	2.75	109
5	4	2.05	192
6	2	1.25	156
7	2	0.95	215
8	2	0.66	303
9	2	0.41	458
10	1	0.19	527
11	1	0.09	1 111
12	1	—	—
Total	76	—	—

is four times expectancy, although the finding could be due to chance.

The following brief case reports suggest a relation of TEF to maternal or placental factors.

CASE 1. A 30-year-old woman with a goiter of about 15 years' duration had had nine pregnancies resulting in living children of whom only the seventh is known to have had a congenital

TEF. Pregnancy was characterized by frequent bouts of sore throat with low-grade fever. During the 4th and 5th weeks while traveling by rail during the summer of 1943 she was without drinking water for over 24 hours and developed "heat prostration," with a temperature of 104 to 105°F for 2 days. A third pregnancy, again associated with intermittent

sore throats, ended in the birth of a normal infant. Chronically infected tonsils were subsequently removed with relief of symptoms referable to the throat.

CASE 4 A 38-year-old previously married woman had had two pregnancies resulting in a normal child, and a miscarriage (at 6 weeks) 2 years prior to the birth of a baby with TEF. Hydramnios had been noted as early as the 6th or

TABLE 3 *Esophageal Atresia and Acute Disturbances of Maternal Health*

ACUTE DISTURBANCE	OBSERVED CASES	STAGE OF GESTATION
Pneumonia (Case 7)	1	First trimester
Appendectomy with uterine suspension (Case 6)	1	First month
Attempted abortion — quinine (Case 10)	1	Early in the third month
Sore throat with heat prostration (Case 3)	1	Fourth to fifth week
Acute upper respiratory infections (Case 9)	1	First trimester again in last trimester

7th month, and a 35-lb weight gain had been recorded. The placenta was found to have a velamentous insertion of the cord.

CASE 5 A 19-year-old primipara, who had had pyelitis treated with a "sulfa drug" from early pregnancy, delivered an infant with TEF.

CASE 6 A 19-year-old primipara, who had undergone an operation for appendicitis and correction of a "tipped womb" in the 1st month of pregnancy, gave birth to the defective infant.

CASE 7 A 24-year-old mother, whose one previous pregnancy had ended normally, developed pneumonia at the end of the 1st month of her next pregnancy. The infection lasted about 4 weeks and was treated with one of the sulfonamides. At term the baby was found to have TEF.

CASE 8 A 48-year-old woman had had 11 living children and 6 miscarriages. She had been operated upon for a ruptured appendix and for goiter during the 3 years preceding the 18th pregnancy, which was complicated by symptoms of pre-eclampsia and resulted in a defective infant.

CASE 9 The third pregnancy of a 35-year-old woman whose previous 2 children were normal resulted in a baby with TEF. She had suffered from a severe cold and cough during the first and "grippe" during the last trimester of gestation. Subsequently a fourth, normal child was born.

CASE 10* The mother stated that she had taken 30 pills of quinine sulfate (30 gm.) early in the 3rd month of her pregnancy to induce abortion.

The same data that suggest a relation between TEF and an unusual placental environment raise the possibility that the fetal disease is secondary to disturbances of the maternal organism or placenta. As long ago as 1867 Dareste¹⁵ described thermal injuries of the developing hen's egg, which resulted in arrested growth of the enveloping membranes. Such arrests preceded development of ocular, cardiac and other abnormalities of the embryo. Moreover, Mall¹⁶ (1908), after a lifetime investigation of the subject, concluded that faulty placentation — as manifested, for example, in ectopic pregnancy — was

the most important causative factor of acquired maldevelopment in human embryos.

Though placenta previa, placenta accreta, circumvallate placenta and velamentous insertion of the cord were each found only once, the collective finding is provocative. It is reasonable to infer that cases of ante-partum bleeding also represented similar specific placental disorders. The association of placenta previa with ante-partum bleeding and an increased incidence of fetal defects has been established by many investigations.^{5, 17} According to Irving,¹⁸ placenta accreta probably results from an imperfect development of the decidua, and "as in placenta previa the frequent bearing of children seems to be an etiologic factor." Williams¹⁹ describes the velamentous insertion of the cord as occurring "comparatively often (9 twins to 1 single) in twin pregnancy, and in single ovum twins is supposed to play a part in the production of hydramnios." Of 47 cases of circumvallate placenta studied by Hunt and his co-workers,²⁰ 15 were characterized by free or spotty vaginal bleeding or drainage of amniotic fluid before the fourth month of gestation.

TABLE 4 *Esophageal Atresia and Placental Conditions in 29 Pregnancies*

CONDITION	RATE PER 1000 LIVE BIRTHS		
	CASES	OBSERVED	EXPECTED*
Hydramnion	20	230	2.5
Ante partum vaginal hemorrhage†	6	69	—
Twin placenta	4	46	10.6
Placenta previa	1	11.4	5.5
Placenta accreta	1	11.4	0.25
Placenta circumvallata	1	11.4	3.30
Placenta velamentosa	1	11.4	8.40

*Figures from various sources.^{5, 17, 20}

†Defined as staining into the 2nd month at 1.2 months 'until 6 months' at the 6th or 7th weeks at the 8th month — considerable and for the first 3 months.

Fetal mortality was 50 per cent. The authors believe the placenta becomes cup-shaped because of early degenerative changes along the border that interfere with the blood supply of the fetus. In compensation, villi grow beneath and beyond the fibrous limit of the frondosum and are covered by the chorionic membrane. The heaped-up villi surround the margin of the placenta until increasing tension causes tears, bleeding or seepage of amniotic fluid. Unquestionably, such placental diseases could affect the nutrition or oxygenation of the fetus although it is impossible to estimate the role played by each of the multiple factors possibly involved,²¹ such as anoxia and vitamin deficiencies.²²

EMBRYOLOGY†

Fully 90 per cent of the cases under discussion present a single, definite pattern. There is a per-

†We are indebted to Dr. F. T. Lewis of the Department of Anatomy, Harvard Medical School for the preparation of this section and permission to use Figure 4.

sistent communication between the trachea, near its bifurcation, and the esophagus, and just above this fistula there is a transverse division of the esophagus that is abnormal at any stage of development. An embryologic interpretation of this combination is all that can be attempted here. Apparently, the first case of the anomaly to be reported in a young embryo was found in what Minot²³ regarded as



FIGURE 3 Sagittal Section of a Human Embryo of 181 mm, with atresia of the Esophagus and Tracheoesophageal Fistula. The full length of the blind upper segment of the esophagus is not included, but the portion of the trachea from its fistula to the bronchial bifurcation is shown. The lower segment of the esophagus, in a fusiform dilatation passes out of the section before reaching the diaphragm (Harvard Embryological Collection, Series 1129, Section 171.)

a normal specimen of 181 mm, with an estimated age of forty days. At that stage the abnormality was as fully established as at birth (Fig. 3), and the writer who discovered it sought its explanation in much younger embryos.²⁴

Broman,²⁵ in his monograph on the development of the omental bursa, had reported that in human embryos of 34 mm, the common cleft-like cavity that later becomes vertically subdivided into the ventral trachea and the dorsal esophagus is closely flanked on either side by similar extensions of the peritoneal cavities. These extensions he named significantly the right and left "pneumatoenteric recesses," but without recognizing their possible relation to the fistula and atresia. Any fluid that they contain would be separated from that within

the amnion and within the yolk sac, but at that age it would not be separated from subplacental and within the chorion. By connection with the pericardial cavity the contents of the recesses might be subject to pressure changes as the heart filled and emptied. Compression of the foregut between the recesses could divide the esophagus along their dorsal borders and produce the characteristic anomaly under discussion. They change in form rapidly, as the left one disappears and the right gives rise to the superior recess of the omental bursa. In an older embryo, which still measured only 3 mm, Broman has shown the anterior ends of these recesses crossing the esophagus, and yet already below the site of the anomaly.

An embryo of 4 mm, figured as a whole by Bremer,²⁶ who clearly reconstructed most of its

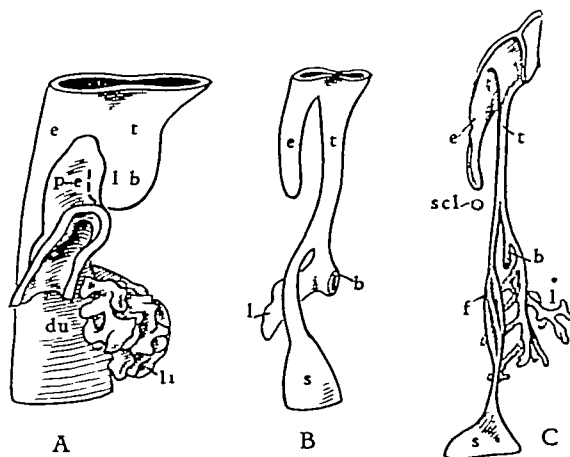


FIGURE 4 Semischematic Lateral Views of Models of Human Embryos, Showing the Development of the Anomaly

A—40-mm normal (?) embryo modeled by F. T. Lewis, B—normal 8-mm stage (Broman²⁵), with the anomaly added, and C—the 181-mm specimen (Fig. 3) modeled by Dr. Albert F. Boretti. In A the esophagus (e) is still undivided from the trachea (t), to which the pyriform lung bud (lb) is appended. P-e demonstrates the right member of the paired pneumatoenteric recesses, undue pressure in which may produce the anomaly. du = duodenum, l = liver. In B, e = upper segment of the esophagus, t = trachea, b = right bronchus, l = left lung, and s = stomach. In C, as in B, with scl, where the anomalous right subclavian artery arises, f = a fusiform dilatation of the lower segment of the esophagus, above the collapsed stomach (s).

organs, is used in Figure 4A to show how the associated atresia and fistula presumably arise. Malformation of the pneumatoenteric recesses, perhaps with undue pressure from their contents, in a brief period toward the close of the first month, could produce it. At 8 mm it should be well established (Fig. 4B). In a misshapen 8-mm thoracopagus Ysander²⁷ has figured mirror-image cases, one in each thorax of the double monster, but since the "bronchi show repeated branching," the specimen is surely stunted. The general relations in

our 18 1-mm specimen are shown in Figure 4C a very similar 19-mm anomaly has been described by Gladstone²⁸

Formerly, the anomalous occlusion of the human esophagus was ascribed to pressure from the neighboring arteries. The dorsal aortas, converging to join behind the intestinal tract, meet at first at too low a level to obstruct the esophagus (a comparison with the description of Congdon²⁹ is of interest). Later, as the lengthening trachea and esophagus push down through their vascular encirclement, the fork formed by the junction of the two dorsal aortas comes to lie in the gap between the upper and lower segments of the anomalous esophagus. There, free from the resistance usually encountered, it has a marked tendency to persist as the "low

TABLE 5 *Number of Synchronisms Observed among 55 Infants with Tracheoesophageal Fistula*

CONDITION	No OF CASES
Cardiovascular system	38
Interventricular septal defect	8
Dextroaorta	4
Coarctation of aorta	3
Others*	23
Gastrointestinal system	33
Meckel's diverticulum	11
Atresia ani	7
Aberrant or anomalous pancreas	6
Duodenal stenosis	4
Persistent cloaca	2
Others	23
Genitourinary system	35
Ureteral dysplasias	6
Horseshoe kidney	5
Others	24
Respiratory system	10
Anomalies of lobulation	8
Others	2
Skeletal system	9
Hemivertebrae	6
Others	3

*The term "others" includes abnormalities occurring less than three times in this series, and does not include patent foramen ovale or patent ductus arteriosus as anomalies of the cardiovascular system.

origin of the right subclavian artery." Often, it is associated with other anomalies of the arterial trunks, especially of the vertebral arteries (as in the 18 1-mm specimen), which may well affect the general nutrition of the fetus.

Two other consequences of the early transection of the esophagus may be expected—one occasionally and the other frequently. Normally, although the digestive tube is elsewhere pervious throughout, its lumen is temporarily interrupted by epithelial septums in the duodenum, and the anus is imperforate. These occlusions, both of which are present though not yet abnormal in the 18 1-mm specimen, tend to persist. The anal opening should form in embryos of the ninth week (22 to 30 mm), but for some reason still unknown the imperforate condition can persist, and it does so especially in association with an earlier interrupted esophagus.

TERATOLOGY

Coexisting anomalies that are prominent in the syndrome of esophageal atresia and TEF (Table 5) involve entodermal and mesodermal derivatives actively differentiating during the first half of the

second month of embryonic life when the trachea and esophagus are also undergoing rapid development. The significance of such defects may be evaluated in comparison with expected embryologic sequences (Table 6).

Autopsies performed on 70 infants revealed all but 3 to have TEF. Fifty-five had a total of 145 coexisting defects as shown in Table 5, such as dextroaorta, coarctation of the aorta, Meckel's diverticulum, atresia ani, horseshoe kidney and vertebral dysplasias. The findings confirm a previous study of Ipsen and Okkels,³³ who made the reasonable inference that such recurring anomalies originate around the same time as TEF. They reported autopsies of 5 infants with TEF and compared findings of 30 published cases. Over three fourths showed other associated malformations, which the authors called synchronisms, most common were atresia ani and defects in development of the urogenital tubercle, of the hand or of the heart and great vessels. They traced the stages by which the trachea normally develops and differentiates from the esophageal primordium in relation to growth (crown-rump length) of the embryo and discussed the significance of synchronisms as a means of establishing the time of developmental arrest. For example, the coexistence of atresia ani and rectovaginal fistula with TEF was interpreted as a manifestation of synchronous arrests of development about the sixth week of fetal life, before perforation of the anal membrane had taken place and before completion of the partition between the rectum and urogenital sinus.

Although simple arrest of differentiation may serve to explain some of the anomalies listed in Table 6 (such as imperforate anus), additional ablation or dissociation* of the entodermal tissues is necessarily postulated to account for other types (for example, transverse division of the esophagus), which have no counterpart in the normally developing embryo. Proof exists (Figure 3) that TEF may be present as early as the 18 1-mm—or second-month—stage of life, and whatever the mechanisms of pathogenesis, the kinds of anomaly listed in Table 6 suggest the need for clinical study of the events of early pregnancy in the search for causative factors.

DISCUSSION

The nature of both the primary anomaly and the associated defects shows that TEF is determined long before birth, and proof exists that the defect may be present as early as the second month (25-mm to 25 0-mm stage) of embryonic life. Whether the malformation is of genetic or acquired origin is the first problem to be decided.

*This term is defined as follows by Mallory: "The repair of a simple wound in the embryo is always associated with further development of the surrounding parts and in case the process ends in a perfect result normal development still remains with or without regeneration. When however the embryonic tissues become mixed, we have a new condition quite unlike any pathological change found in the adult. This pathological condition I shall term dissociation."

In the combined series of Plass² and ourselves TEF was never recorded as having appeared in successive generations or recurring in the same generations of 243 families. Although the possibility of a genetic origin is not disproved by negative findings, the positive teratologic observations of this study permit the formulation of an alternative hypothesis. On the basis of the morphology of the tracheoesophageal defect and that of associated arrests (Table 5), the syndrome is postulated as acquired during early fetal life — with departure from normal sequences of development (Table 6) occurring at about the fifth or sixth week. If this

demologic findings on which the inference rests await confirmation by others, the biologic principle postulated has been conclusively established for the better part of a century by investigators in the field of experimental zoology.^{15, 37} The teratologic findings in the present study imply that TEF also is a function of host development, for all the recurring synchronisms involve entodermal or mesodermal structures differentiating at the fifth or sixth week of embryonic life.

The lacking evidence necessary to prove a hypothesis that TEF and its synchronisms represent departures from normal development during the

TABLE 6 *Physiologic Events Pertinent to Tracheoesophageal Fistula (Fourth to Eighth Weeks of Fetal Life) **

WEEK	RESPIRATORY SYSTEM	GASTROINTESTINAL SYSTEM	CARDIOVASCULAR SYSTEM	GENITOURINARY SYSTEM	SKELETAL SYSTEM
4th (0.5-2.5 mm.)	Tracheal primordium buds off ventral esophagus and longitudinal grooves appear	The pharynx foregut hindgut, and cloaca comprise the gastrointestinal tract sealed at either end by the pharyngeal and cloacal membranes	Paired aortas with dorsal and ventral components have differentiated from primitive capillary network as heart has become a single tube with atrium, ventricle and bulb	Condensations of mesenchyme form mesonephros with imperforate duct reaching to cloaca	Sclerotomes formed by condensations of mesenchyme about chorda
5th (2.6-5.5 mm.)	Pharyngeal membrane ruptures beginning separation of trachea from esophagus from below upward lung bud appears	Yolk sac separates double primordium of pancreas buds from duodenum cloaca differentiates into anus and urogenital sinus	Primordia of semilunar valves septum primum and septum secundum are evident cardiac chamber intercommunicate freely	Mesonephric ducts develop lumen the primordia of primitive pelvis and ureters	Vertebral cartilages on left side are separated from those of the right by the pericardial septum chondrification of limbs begins.
6th (5.6-11 mm.)	Further lobulation of lungs and formation of bronchi definitive separation of trachea from esophagus occurs	Involution of yolk sac two pancreatic primordia approach each other partitioning of rectum from urogenital sinus completed.	Primordia of cardiac septums develop as heart bends and rotates to right fourth left aortic arch emerges as dominant great vessel descending aortas fuse from 7th intersegmental arteries to bifurcation	Primitive kidneys differentiate close together in urogenital folds below aortic bifurcation ureters elongate and pelvis migrate cephalad toward nephrogenic tissues	Pericardial septum is broken through by hyaline cartilage which unites about chorda carpal and tarsal chondrifications are evident.
7th (12-17 mm.)	Septum between trachea and esophagus has been completed both structures elongate	Fusion of pancreatic primordia results in formation of single organ rectum has developed and anal membrane is present.	Duplication of wall between cardiac limbs lags in development resulting in 3 chambers sinus venosum atrium and ventricle.	Differentiation of calyces and integration of collecting tubules with primitive secretory and vascular units	Articular and laminar processes of vertebrae develop first row of phalanges has differentiated
8th (18-25 mm.)	Lung development continues coincidentally with bronchial differentiation	Yolk sac has atrophied dorsal pancreatic duct disappears and duct of Wirsung develops rupture of anal membrane occurs	Subdivisioning of heart development of valvular apparatus and contours of great vessels largely established.	Further differentiation migration and rotation of kidneys	Further differentiation of cartilaginous skeleton and beginning ossification of previously formed structures

*Sources of data: Dadds³⁸; Keibel³⁹ and Mall⁴⁰ and Arey⁴¹

interpretation is correct the biologic pattern of TEF is analogous to that previously described for mongolism³⁵ except for basic differences in the stages and organs involved by disease.

The principle that a specific agent acting on the embryo may give rise to widely divergent teratologic manifestations in human beings³⁶ as well as animals^{15, 22, 37} has been amply confirmed by observations that numerous cardiac, dental and cerebral synchronisms characterize the syndrome of post-rubella congenital cataract.³³ The facts pertinent to mongolism were interpreted to indicate that a specific clinical defect may be engendered by multiple unrelated agents, and that the particular result was a nonspecific function of the stage (eighth week) of embryonic development — not a specific property of the agent. Although the epi-

early part of the second month of embryonic life caused by agents acting through the mother and placenta relates to their specific identification and demonstration of activity at this period. The kinds of agent to be considered and tested as possible causes of prenatal disease of the conceptus have been the subject of study by Ingalls and Gordon.²¹ Agents were grouped in three categories: infectious (rubella, syphilis), chemical (nutritional deficiencies, toxic and metabolic disturbances) and physical (mechanical trauma, structural disease of the uterus). A relatively high incidence of maternal illegitimacy observed in this series, if confirmed, would suggest an occasional connection with attempted abortion — with the agent either mechanical or chemical (quinine in Case 10). A possible connection with spontaneous threatened abortion

(and the agents that produce it) is suggested by the finding that 6 of 29 mothers had ante-partum vaginal bleeding. Five of these 6 bled during the first trimester of pregnancy. That infectious agents are involved in some cases is suggested by the fact that 5 of the 6 cases of acute illness were localized in early pregnancy instead of being scattered throughout. Such evidence is necessarily fragmentary and inconclusive, for TEF occurs rarely, 100 cases such as those assembled here representing the product of about half a million births. The future investigation of such a rare condition lies with the large lying-in hospital. If the mother's prenatal course has not been recorded in satisfactory detail it should be reviewed immediately after the baby is born—before the events of early pregnancy are no longer accessible. We hope that this article will prompt physicians to record and publish further data by which the hypothesis set forward here can be either confirmed or discarded. The question at issue is not merely the etiology of a rare syndrome but also principles underlying cause and prevention of all malformations acquired during prenatal life.²¹ It is likewise increasingly evident that the basic problem is not clinical, embryologic, bacteriologic, biochemical or genetic, but an aggregate of those disciplines, which includes also application of epidemiologic and statistical methods.

SUMMARY

The causative agents of congenital atresia of the esophagus must be primarily genetic or else acquired during prenatal life because the defect is present at birth. A review of the records of 107 infants with the condition revealed no case in which the defect appeared in successive generations or recurred in the same generations of a family, 102 of the infants had an associated tracheoesophageal fistula (TEF) and significant associations were also observed with anomalies of the cardiovascular, gastrointestinal, genitourinary, respiratory and skeletal systems. On the basis of the morphology of the tracheoesophageal defect and that of associated arrests the syndrome is postulated as acquired during early fetal life—with departures from normal sequences of development occurring at about the fifth or sixth week. If this interpretation is correct the biologic pattern of TEF is analogous to that previously described for mongolism except for basic differences in the stages and organs involved by disease.

A study of maternal factors confirmed previous observations of a significant association with hydramnios. Twins were encountered in 4 cases, 6 mothers had ante-partum hemorrhage (5 in the first or second month), and 6 also suffered acute infections or metabolic disturbances in the first trimester of pregnancy.

The hypothesis is made that esophageal atresia, tracheoesophageal fistula and certain commonly

associated defects represent departures from normal development about the fifth or sixth week of embryonic life caused by agents acting through the mother and placenta. This hypothesis should be tested by future observations since the question at issue not only is one of specific etiology but also involves principles underlying the larger phenomenon of acquired congenital malformations.

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The heart is moderately enlarged, globular and extremely soft and flabby. It measures 15 by 13 by 6 cm and weighs 450 gm. The epicardial surface is slightly dull and presents a few dark-crimson petechiae, particularly on the posterior surface. There is a moderate amount of subepicardial fat. The myocardium is soft, flabby and light red brown. The endocardium is smooth and glistening. The coronary arteries are soft and patent. There is minimal fusion of the commissures of the cusps of the aortic valve, with slight thickening of the cusps near the commissures. Histologic sections of the heart show the pericardium at points to be covered with fairly old, unorganized fibrin. The underlying pericardium contains diffuse and focal infiltrations of moderate numbers of lymphocytes, histio-

myocardium, cardiovascular collapse (shock and decompensation), pulmonary congestion and edema, slight, marked passive congestion of the liver, spleen, kidneys and intestine, moderate cerebral congestion and edema, bilateral hydrothorax, slight retroperitoneal edema, focal necrosis and fatty degeneration of the liver, dilatation of the stomach, calcified mesenteric lymph node, slight aortic atherosclerosis and old, healed appendectomy scar.

DISCUSSION

In 1948 O'Hallaren and Lemere¹ reported 2323 cases of conditioned-reflex treatment of chronic alcoholism with emetine without a warning of the dangers to the heart. They state that "the treatment is a safe procedure if administered by properly trained personnel." They report 3 deaths, 1 from congestive heart failure and 2 from coronary occlusion. They present no program to prevent such a tragedy as is reported above. The safety of this procedure could be increased if the properly trained personnel is on the alert for signs of cardiac toxicity.

In 1947 Dack and Moloshok² brought the literature up to date but reported no deaths specifically cardiac in origin. Six deaths were described as occurring after a total of only 0.6 gm (10 gr), but the majority followed 1.2 gm (20 gr) or more. The patient in the case reported below received 0.75 gm (12.5 gr) hypodermically, in addition to a small amount by mouth several minutes prior to vomiting.

Electrocardiographic changes after administration have been reported as follows: ventricular fibrillation (in rabbits)³, intraventricular block, inversion of T waves and cardiac arrhythmias (in experimental intoxication in cats)⁴, T-wave depressions in all leads, chiefly in the limb leads in man⁵, a T wave of the coronary type in Lead I, with precordial pain persisting for about an hour in man⁵, auricular fibrillation after six daily injections of 0.02 gm ($\frac{1}{2}$ gr) in man⁶, ventricular tachycardia and finally ventricular fibrillation in rabbits—the minimal intravenous lethal dose in these animals is about 2 mg per pound of body weight⁷, increase in auriculoventricular conduction in man⁸, and premature systoles, both auricular and ventricular but ventricular predominantly in man⁸.

These changes are evidently reversible if the subject survives. Berman and Leake⁷ found no marked permanent changes in tracings after daily intravenous injections approximately equivalent to 1 mg per pound of body weight in rabbits.

Boyd and Scherf⁴ observed that electrocardiographic alterations gradually disappear within forty-five minutes in dogs. However, Klatskin and Friedman⁸ and Dack and Moloshok² reported that in man abnormalities persisted for two months or more.

Though most of the experimental investigation has been in animals, several writers have studied the cardiologic effects of emetine in patients with amebic dysentery treated with the drug. Hardgrove and Smith² studied 72 patients with dysentery in the Canal Zone receiving 0.6 gm of the



FIGURE 2 Section of the Apical Portion of the Right Ventricle (Phloxine and Methylene Blue Stain $\times 133$)

cytes and plasma cells. At points in the pericardium are small foci of extravasated erythrocytes accompanied by a small number of neutrophils. The myocardium throughout is slightly edematous, and large numbers of muscle cells contain minute fat vacuoles. Occasional muscle cells are undergoing ischemic necrosis and are being infiltrated with histiocytes, lymphocytes or rarely by neutrophils. The tissue planes of the myocardium are infiltrated with small numbers of lymphocytes, histiocytes and rare plasma cells and eosinophils, this cellular infiltration is more marked in the right ventricle than in the left (Fig. 2). Sections of the anterior descending coronary artery show a slight intimal fibrosis, with a very small amount of atheromatous debris. Sections of the conduction system are not remarkable.

There is marked acute passive congestion of the liver, spleen, kidneys and intestine. There is moderate cerebral congestion and edema and slight passive congestion and edema. Each pleural cavity contains approximately 400 cc of clear fluid.

The final diagnoses were toxic myocarditis, chronic fibrinous pericarditis with petechiae, chronic myocarditis with focal necrosis, fatty degeneration and edema of the

drug in ten days. They found minor electrocardiographic changes in 52.7 per cent but concluded that with these doses emetine is not dangerous — though electrocardiographic studies should be made before, during and after treatment. The delayed appearance of electrocardiographic abnormalities must be stressed. Dack and Moloshok² described changes often delayed until one or two weeks after discontinuation of the treatment as in the case reported above. They conclude that absence of electrocardiographic changes during treatment does not warrant continuing the drug beyond a certain dose. Klatzkin and Friedman⁸ concluded that toxic manifestations may occur at any level of dosage depending on individual susceptibility to the drug. They found that the drug is cumulative in the myocardium and that rest periods between courses of the drug should therefore be adequate.

Rinehart and Anderson⁹ have studied the effect of emetine on cardiac muscle in rabbits. They found lesions similar to the Aschoff reaction of acute rheumatic fever. The changes were both acute and chronic. The former consisted of interstitial edema of the muscle, and the latter of necrosis of fibers and degenerative swelling. Focal proliferation of interstitial tissue resulted in response to necrosis of muscle fibers. Lymphocytes, plasma cells, eosinophils and polymorphonuclear neutrophils were found in such foci. Nuclei of muscle fibers showed changes in size and distribution of chromatin interpreted as evidence of injury. Small cellular scars about necrotic muscle fibers were found in chronic intoxication. The lesions were of distinctly greater severity in the heart than in skeletal muscle or liver.

There is no known specific treatment for the cardiac damage due to emetine. One is left with symptomatic management and the usual measures for the handling of cardiac failure, which include rest, sedation, plasma, oxygen, salt-free diet and the judicious use of digitalis and quinidine. Prevention is all important. It is suggested that rules be set up to govern all patients being given conditioned-reflex treatment for alcoholism by means of emetine. Experience of others and the lack of cardiac supervision of this case during treatment suggest the following rules as minimum require-

ments: an electrocardiogram should be taken before, during and one or two weeks after treatment; suspected organic heart disease should contraindicate treatment; the total dose of emetine should not exceed 0.6 gm (10 gr) in any one course; at least two months should elapse between courses of treatment in patients who show any electrocardiographic changes during treatment; when significant electrocardiographic changes occur, treatment should be stopped at once, and signs of toxicity — namely, diarrhea, fatigue, dyspnea, muscular tremors or weakness — and dizziness should be carefully watched for daily, and if these develop the heart should be watched with great care (an increasing tachycardia with the patient at rest calls for at least temporary cessation of treatment).

The prognosis in these cases is good if the early signs of cardiac damage have been heeded, since the pathologic process is reversible.

SUMMARY

A death apparently due to the toxic action of emetine on the myocardium is reported. The drug was used in the conditioned-reflex treatment of chronic alcoholism in a healthy young man.

A program designed to prevent a recurrence of such a tragedy is suggested.

A dosage limit of 0.6 gm (10 gr) in any one course should not be exceeded.

65 Sterling Street

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MEDICAL CARE FOR THE AMERICAN PEOPLE*

Is Compulsory Health Insurance the Solution?

LELAND S. McKITTRICK, M.D.†

BROOKLINE, MASSACHUSETTS

MR OSCAR R. EWING, Federal Security Administrator, in his report to the President¹ urges compulsory Government health insurance as an essential part of a long-range program to improve the health of the nation. He points out that the 5,000,000 men rejected by the draft as unfit for the armed forces, the 4,300,000 man years of work lost through bad health and the national loss of \$27,000,000 in national wealth through sickness and partial and total disability are evidences of the bad state of the national health, and that at least 70,000,000 people in this country will have difficulty in providing adequate minimal medical care for themselves and their families.

How do these more prominent reasons for the establishment of a federal insurance program stand up under factual analysis? Is there a real need for such a program? If not, what are the more important reasons for opposing it at this time?

Will Compulsory Health Insurance Improve the Nation's Health?

We, as physicians, recognize the need for continually improving the many factors that contribute to better health. But are we, and is the public, properly informed when we are told that the way to better health is through compulsory health insurance? The following quotation from Simons and Sinai² is most instructive.

When insurance systems are being urged upon governments, one of the strongest arguments offered is that improvement in general health will follow prompt, universal medical care. After the system has been adopted, one of the most amazing things to the outside observer is the almost complete absence in the vast amount of discussion of any reference to public health in relation to insurance. Moreover, not even the most intense partisan of insurance has ever attempted to present any statistical proof that insurance has any effect upon the general death- and sickness-rate. No sort of statistical manipulation has ever been able to show any correlation between the movements of death-rate in insurance and non-insurance countries. They have declined in both at about equal rate, according to sanitary and health measures and other influences, but no difference in any way traceable to insurance can be discovered.

This is the more remarkable since water protection, better housing, tuberculosis care, isolation, immunization, and numerous other health measures do show such traceable results. At no point has a disappointment been greater than in the failure of insurance as a preventive measure.

Contrary to all prediction, the most startling fact about the vital statistics of insurance countries is the steady and

fairly rapid rate of increase in the number of days the average person is sick annually and the continuously increasing duration of such sickness.

The average recorded sickness for each person per year practically doubled in Great Britain and Germany after the installation of Government insurance.² What evidence does Mr. Ewing have to suggest that the effect of Government insurance upon work days lost through sickness will be any different in this country than in others?

We still read that the high percentage of rejections in the military recruitment program has provided striking evidence of the unsatisfactory state of the nation's health and that for this reason a national health insurance program is essential. We, as physicians, know that there are millions of men in this country in good health who will not meet the rigid requirements for combat duty in the armed forces. We know that at least 80 per cent of those rejected could not have been rehabilitated by any medical care known at this time, and we know that of the approximately 20 per cent who might have been influenced by medical care, it would have been necessary for them to have consulted the doctor, to have accepted his recommendation and for the treatment to have been completely successful.³

We, as a profession, are the first to recognize the importance of improved sanitation and other public-health measures. They are fundamental to any program to improve the nation's health, but provision of these is in no way dependent upon or to be confused with a compulsory health insurance program.

Is Compulsory Health Insurance Necessary to Provide Medical Care to Half the Population?

What are the facts concerning the "70,000,000 people" who "will have difficulty in providing adequate minimal care for themselves and their families"?

About 28 per cent of the families of this country had incomes under \$2000 in 1946.⁴ Many of these can pay nothing or only a portion of the cost of a serious illness. The indigent are provided for in the present Administration bill (S 5) only when "equitable reimbursements to the account on behalf of such needy or other individuals have been made, or for which reasonable assurance of such reimbursements has been given, by public agencies of the United States, the several states" and so forth. The same agencies could readily purchase such care

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†Clinical professor of surgery, Harvard Medical School; surgeon in chief, Palmer Memorial Hospital; visiting surgeon, Massachusetts General Hospital.

from medical care programs already in existence or in process of formation. There is, then, no need for a compulsory Government health insurance agency to assure proper care for this group.

Approximately 50 per cent of our families are now earning between \$2000 and \$5000 a year. Good medical care is and will remain costly. The total expenses associated with a serious illness are too high for most of these families to meet without difficulty at the time of the sickness. However, many own automobiles, television sets and electric refrigerators, and, as a group, they spend a large amount on alcoholic beverages and other things. These are accepted as a part of the American life. But, at the same time, if these families had to pay cash for their automobiles, for their electric refrigerators or for their television or radio sets, many would not be in a position to buy them. Is it fair to say that because they cannot pay cash for these items they cannot afford them? Because this same group cannot pay for a major illness at the time it occurs is it just to assume that they cannot afford to pay for it? Because a mechanism to spread the costs of serious illness must be made available to these families, why must it be done under the costly, inflexible and inefficient machinery of federal Government before thorough exploration of reasonable alternatives?

We need have no great concern for those with incomes over \$5000, although we must also accept the fact that it is customary for most of us to adjust our standards of living pretty well to our incomes, to the end that many families with annual incomes between \$5000 and \$10,000 will have difficulty in paying large medical bills at the time at which they are incurred. Many of these recognize the importance of spreading the cost of illness, and for them such a mechanism would be a convenience though not a necessity.

We have now in this country the highest quality of medical care, the best teaching and the most productive research of any country anywhere. As the science of medicine has improved to make this possible, the costs have increased. We have not developed a satisfactory means of paying these increased costs. Industry was faced with, and successfully met, a similar problem in selling its technical products. Because we as a profession have failed to lead the way, we as a nation are now being urged to make a complete change from a system of medical practice that places emphasis on quality of service and direct responsibility to the individual and his family, to a system that had its concept in the Bismarckian philosophy, which puts emphasis on quantity rather than quality, and which fixes the ultimate responsibility of the physician to the central Government rather than to the patient.

We are unable to find any factual evidence to support the contention that compulsory health insurance will improve the health of the nation. A

sound program to afford medical care to the needy is not dependent upon a Government insurance system. There is urgent need for developing a method of paying for the medical care of the large segment of our population who cannot, or would prefer not to, meet the payment for serious illness when it comes. Does our failure to have provided a mechanism for doing this justify a complete change from any possible solution of this problem on a voluntary basis to a system of compulsion that has been tried in so many foreign countries and has as yet provided no country with the quality of medical care equal to ours?

Does Compulsory Health Insurance Meet the Qualifications of a Good Medical Care Plan?

Without careful analysis it might seem very reasonable for all of us to pay a tax to the federal Government, which, in turn, takes the responsibility of supplying us with and paying for our medical care whenever we need it. It is a very easy matter, in writing, from the platform or over the air, to develop a logical and apparently practical program. It must be remembered, however, that a successful program to provide prepaid medical care is dependent upon certain fundamental principles. The more important of these are free choice of physician, mutual co-operation of the public, those rendering professional services and the administrative agencies, continuing improvement in the quality of care given, the teaching in medical schools and research, and a total cost of the program in keeping with the general economy of the community.

Free choice of physician. Only a short time ago Mr. Ewing⁵ assured the public that from the patient's point of view there was absolutely no difference between the present system and that which the Administration was proposing (compulsory health insurance) except that the Government would pay the bill. If this is true it means that you as a patient can go to any physician you wish at any time, provided he is available and is willing to accept you. At present he is limited in the number of patients he can care for only by the number who seek his services or by the number of working hours in his week. Since those who can be expected to pay for his services, he is spared a multitude of demands upon his time for minor, insignificant complaints. The fact that longer hours mean greater income is an incentive for him to be available to prospective patients throughout most of each twenty-four hours. Mr. Ewing knows and his advisers know that a medical care plan of the magnitude proposed cannot remain solvent if the physician is paid each time he sees a patient. They know that removal of any financial responsibility from the patient will greatly increase the demands upon the physician's time for unimportant complaints. They know that the number of patients a physician will

be permitted to care for must be limited. Every prospective patient in a community must register and have his name on some doctor's panel. The best known doctor in each community will be in the greatest demand, and in fairness to all, those first applying must be accepted until the panel is filled. When his panel is filled, all others desirous of being under his care must select another doctor or will be assigned to one by those responsible for carrying out the plan. Moreover, there will undoubtedly be a certain number of the most successful and older physicians in each area who may well prefer not to become part of such a program. Under compulsory health insurance the free choice of physician cannot be assured to anywhere near the degree that it is available at the present time.

Co-operation. Co-operation between those giving, those receiving and those administering any plan is essential. Co-operation means mutual confidence and mutual respect.

We hear Mr. Ewing⁵ over the public radio say that there will be absolutely no change in the relationship between the patient and the doctor, except that the Government pays the bill, and that the maximum payment that anyone will have to meet is \$1.40 per week. We know that it will be absolutely impossible to maintain, under a Government program, the private practice of medicine as it now exists. We know, and Mr. Ewing should know, that a maximum of \$1.40 per week on the part of the worker, in addition to a like amount from the employer, cannot possibly support the comprehensive program outlined. Such statements are misleading and do not inspire the confidence of an enlightened public or of the medical profession.

Mr. Ewing¹ states that there are 325,000 lives lost in this country each year that we have the knowledge to save. We are not told the basis for these figures, but we read that 117,000 of these lives are lost through heart disease and cancer. We know that the death rate for heart disease among the physicians of the country is higher than it is in the population at large.⁶ We do not believe that lack of medical care is responsible for the greater number of our profession who die each year of this condition, and therefore we fail to understand how a compulsory health insurance program will help save the lives of others who have heart disease. We know that in the state of Massachusetts only 0.3 per cent⁷ of those coming to our cancer clinics have delayed in coming because of economic reasons. We do not know how to make an earlier diagnosis of cancer of the internal organs, many of which give symptoms too late for cure. We do not know how to remove from the patient the fear of reality, dread of an operation and other factors that postpone early diagnosis and treatment of cancer. We are certain that the introduction of a compulsory health insurance program will not alter these factors and therefore

will have little effect upon the death rate from this disease.

We are, therefore, at a loss to understand the basis for Mr. Ewing's figures or how we, as a medical profession, can have confidence in an agency and its administrator that are responsible for giving to the public this kind of information. Nor do we understand how Mr. Ewing can have confidence in and co-operate with a profession of which he says, "Which is the more important? The personal, selfish business and professional values of 180,000 practicing physicians in this country, or the health and well-being of some 68,000,000 of our population?"⁸

Surely there is nothing in the material discussed above to assure the type of mutual confidence and respect that is essential to the smooth running of so important a program.

Quality of care. Whenever compulsory health coverage has been adopted, the emphasis has been on quantity and not on quality of care. This was so in Germany, was and is so in England, is so in New Zealand, and, if adopted, it will be so here. Unethical though it may be, it is common practice to get everything possible from anything as remote from the individual and as wealthy as a government. Seeing too many people with minor transient complaints and nothing wrong dulls the doctor's perception for the early signs of serious disease. History taking and examinations become superficial and a matter of routine.

Good medical care cannot be assured by legislation or by any mechanism of payment. It is personal, individual and intangible, and it depends not only on the training and experience of the physician, upon his scientific accomplishments and facilities but, more than anything else, upon the intensity and thoughtfulness with which he applies these to the individual patient who is sick. A feeling of responsibility directly to the patient and to his family, as well as ethical competition between physicians for the confidence of the public, is the more important factor in assuring each patient the personal care that he wants from his doctor. Any third party coming between the patient and his physician may interfere with this relationship, but when Government assumes complete responsibility for paying the physician and for providing medical care to the patient, such a relationship cannot survive.

It is difficult to foresee just how far reaching the effect of compulsory health insurance might be upon the actual care of the more complicated illnesses. What, if any, effect might it have upon the training of young men in preparation for the actual care of the sick? To those of us who are actively interested in preparing young men for the specialties, it is disturbing to learn that in New Zealand many desirable young doctors are not being attracted to the ranks of the future specialists and

teachers because the "unnaturally swollen rewards of general practice"⁹ can be enjoyed after a much shorter and less arduous period of training than that necessary to qualify them for the all-important responsibilities of the specialists and of teaching.

The cost Compulsory health insurance, as now advocated, is not insurance. There is no calculated risk, no payment of a premium to cover the cost of specific benefits and no contract. It is a form of taxation and should be recognized as such.

Comprehensive medical care is not an insurable risk. The demands upon such a program will be unlimited, indeterminate and uncontrollable. Abuse of the privileges is easy and attractive and therefore likely. The cost will be unpredictable and inordinately high.

In Berlin, the cost for sickness insurance almost doubled per member in the five years between 1925 and 1930,¹⁰ resulting in the "Emergency Decree" of July, 1930. In New Zealand,¹¹ the total income from social-security taxes in 1945-1946 amounted to 15,000,000 pounds, and it was necessary to take 7,000,000 pounds from the consolidated fund to meet the total expenses of the social-security program. One year later, in the budget for 1946-1947, it was expected that 20,000,000 pounds would be received from the social-security taxes, owing to an increase in the rate. But during this year it was anticipated that 18,000,000 pounds, an amount almost equal to the total income of the social-security agency, would be taken from the consolidated fund to meet the expenses. This represents a social-security budget of 38,000,000 pounds, or 60 per cent of the revenue from all sources for the previous year.

In England, three months after the beginning of the present health program, Mr. Bevan made the following statement:

Because things are free is no reason why people should abuse these opportunities. This is a great test of the maturity of the British people in so far as they have all of the resources of the medical profession at their disposal without charge. If any individual abuses the opportunity, he must reckon with a sum total which might add up to one too grievous to carry and for which it would be very difficult to continue to provide.

Two months before the end of the fiscal year the Ministry of Health asked for \$233,820,000 in addition to the original estimate of \$598,700,000 to meet the expenses of the program for the first nine months.¹²

We find little to comfort us in the report of the subcommittee of the Hoover Commission,¹³ which studied the medical care program for which the Government is now responsible. The many evidences of extravagance and waste in money and in manpower are forcefully presented—for example, the Government pays \$20,000 to \$51,000 per bed for construction of hospitals in areas where voluntary hospitals are doing this for \$16,000 per bed. In the New York area, hospitals contemplated

or under construction will approximate a cost of \$105,200,000, which the commission, after careful investigation, finds it difficult to justify. In Houston, Texas, the Veterans Administration is letting bids for a 1000-bed hospital at an estimated cost of \$25,000,000, which the Commission believes would be unnecessary if the unoccupied beds in other governmental hospitals in that area were utilized. Evidence of the effect of the "free" hospital care of a Government-controlled program upon its cost is found in a comparison of the length of stay of patients after similar operations in voluntary and in Government hospitals (Table 1).

Not only is the actual cost for the care of each illness much greater in the Veterans Administration than in voluntary hospitals, but also the longer

TABLE 1 *Average Hospital Stay in Voluntary and Government Hospitals*

OPERATIVE PROCEDURE	AVERAGE HOSPITAL STAY	
	VOLUNTARY GENERAL HOSPITALS	VETERANS ADMINISTRATION HOSPITALS
	days	days
Appendectomy	7.8	14.3
Tonsillectomy	1.4	15.1
Hemorrhoidectomy	6.9	34.5
Herniotomy (inguinal)	10.5	27.0

stay means that more beds are necessary to take care of the same number of patients. More beds means more construction, more personnel, more cost.

The people of this country must realize that there is no such thing as mass production of medical services. Each examination, whether x-ray or clinical study of the patient, is a personal service and one that takes time, and will remain costly if well done, even under the most efficient type of program. Such a program as advocated by Mr. Ewing cannot possibly be paid for by payroll deduction but may necessitate a bottomless pit with limitless money. This can only mean a tax burden out of all proportion to the benefits received.

Free choice of physician, co-operation, continuing improvement in the quality of care given and a total cost in keeping with the local and national economy cannot be expected if compulsory health insurance is adopted. Because we believe these to be essential to a successful medical care plan, we are opposed to compulsory health insurance until sincere and co-ordinated efforts to attain these objectives by other means are made and found wanting.

Off with the Old, on with the New?

There are many who are very close to the problem of bringing good medical care to the American people who believe that a country so large and so diversified as ours may not lend itself to any single

over-all plan, that our objective should be to provide the most widespread distribution of the best available medical care at the lowest cost possible, that our planning should be concentrated upon the end rather than the means, and that only through programs carefully planned and efficiently administered will we later have the experience and background necessary to put into effect that program which most nearly meets these objectives. The adoption of compulsory health insurance would eliminate any possibility of experimentation outside the structure of the compulsory, centrally controlled plan. "Once the whole employed population, wives and children included, is brought within the scope of compulsory sickness insurance, the great majority of doctors, dentists, nurses, and hospitals find themselves engaged in the insurance medical service which squeezes out most of the private practice on the one hand, and most of the medical care heretofore given by public authorities on the other. The next step to a single national medical service is a short one."¹⁵ Are we ready to discard completely the tremendous advances made by non-profit and commercial agencies during the past ten years, or should our efforts be intensified to eliminate the many defects now recognized in present plans with the expectation that from these experiences will evolve a program that will be practical, effective, efficient and available to all who desire it?

Who Shall Be Our Keeper?

When we as a nation become dependent upon the Government for our medical care we come to think of the Government as a paternal agency to which we turn and upon which we become increasingly dependent. Bismarck recognized the importance of this when he put a compulsory health insurance program into effect in 1883. Since that time the adoption of a compulsory, Government-controlled medical care program has been one of the most important early steps in the more complete socialization of a country. This was so in Germany, and it is so in England and in New Zealand. If this is the will of the American people, it should be so here, but we should be remiss if we did not point out the implications of making the Government rather than ourselves responsible for anything so personal and so essential as medical care. We are told that this is not socialized medicine, that it is no different from "buying fire insurance" (Ewing). But when the Government takes complete responsibility for providing a service, when we are compelled to pay a tax to the Government for that service, and when the Government in turn regulates and pays those who provide it, that

service is socialized and is subject to the evils of political control

* * *

There is little evidence that compulsory health insurance will improve the health of the nation or that it is necessary to assure adequate medical care to the American people. There is much to suggest that such a program would gradually lower rather than continue to improve the quality of care received and that its cost would be inordinately high. We therefore oppose its adoption.

We believe that provision of adequate medical care for those unable to obtain it by voluntary prepayment plans or by direct payment is the responsibility of local or state government aided by charitable agencies and, if necessary, by federal grants-in-aid to state programs. Such a program is in no way dependent on compulsory health insurance.¹⁶

We recognize the necessity of spreading the cost of serious illness by the development of more effective voluntary plans than those available today. We believe that the medical care of those able to purchase it through such plans or by direct payment is the responsibility of the individual, not of the Government.¹⁶

The development and perfection of a complete medical care program presents many problems the solution of which is not yet at hand. However, the rapid advances in medical care during the past decade suggest that, given further opportunity and with the complete co-operation of all concerned, — the public, those furnishing the services and the various private and Government agencies, — this country can develop a most effective and efficient medical-care program and still retain the initiative and individual freedom that have made it so great.

1180 Beacon Street

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PRACTICAL ASPECTS OF BETTER MEDICAL CARE*

ARTHUR W. ALLEN, M.D.†

BOSTON

IN A discussion of the plans for better medical service to the people of the United States it seems logical to me that we should take into account what has been accomplished along these lines. We can be justly proud of the fact that the American people have available to them better medical care than the people of any nation in the world. I wish to bring to your attention some of the important factors that have brought this about and to offer some feasible suggestions about how we may still improve this service to humanity.

MEDICAL EDUCATION

The basic principle of good medical care arises in the education of the physician. Thirty-five years ago anyone could choose the medical school that he found the cheapest or nearest to his home or on the basis of the reputation of some of its teachers. Through the efforts of the Council on Medical Education and Hospitals of the American Medical Association, standards were developed for the medical schools of this country. These standards were based on adequate equipment and a proper proportion of full-time teachers. About seventy medical schools in the country meet these requirements, and all but three or four of the ones that could not meet them have ceased to exist. Massachusetts was one of the last states to legislate against the substandard school, with the result that we have a large number of the graduates of such schools practicing in this state. Through the efforts of the graduate teaching program of the Massachusetts Medical Society and the introduction of the so-called Gallupe Plan, which urges hospitals to aid in the education of the physician, these men are becoming well trained, safe and valuable doctors in their communities. A survey is now being made in the eighteen medical districts of the Commonwealth to ascertain the effectiveness of this educational program with the view of expediting the situation as rapidly as possible.

HOSPITALS

Early in the history of the American College of Surgeons it became obvious that the educational background of the surgeon was the hospital in which he received his postgraduate training. On the basis of equipment, laboratories, nursing, records, staff conferences, pathological studies and so forth, standards were set up. A survey of all the hospitals of 100 beds or over in 1922 revealed that less than 13 per cent could fulfill these require-

ments for adequate patient care and adequate resources for the training of the surgeon. By constant effort on the part of the American College of Surgeons 94.6 per cent of these hospitals have now met the standards. If we include the smaller community hospitals down to 25-bed capacity the percentage drops to 90.

THE PUBLIC HEALTH SERVICE

Article II of the Constitution of the American Medical Association states "The objects of the Association are to promote the science and art of medicine and the betterment of public health." The Public Health Service has always had the complete support of the medical profession. The prevention of disease is the first and most important concept of our entire medical care program. I am informed that there are many vacancies in the Public Health Service and that in many communities there are inadequate facilities. To correct these deficiencies we may accomplish our greatest improvement in the program for better medical care of our people.

Smallpox, typhoid fever, malaria, tetanus, scarlet fever and diphtheria took a heavy toll of our forebears. These diseases have been so completely reduced to a minimum that the average medical student may consider himself lucky if he has the opportunity to see a case.

RESEARCH

Through the elevation in standards of medical education and hospital facilities for research many life-saving contributions have been made. Diabetes and pernicious anemia are outstanding in this category. There are hundreds of well trained medical scientists working steadily to discover the cause of cancer, arthritis, multiple sclerosis, arteriosclerosis and many other diseases not yet conquered. The discovery and development of the sulfonamides, penicillin, streptomycin and other antibiotics has lowered the incidence of death from pneumonia, peritonitis, septicemia and other illnesses caused by bacteria to a remarkable level. The better understanding of the chemistry of the body and the methods of bringing about a chemical balance in the tissue fluids has contributed greatly to the safety of surgical procedures particularly. Through research we may hope to reduce the incidence of disease and thereby increase life expectancy.

SPECIAL AGENCIES

Here in Massachusetts we are particularly aware of the many voluntary agencies engaged in special

*Presented at the Women's City Club, Boston, February 1, 1949.
†Consultant in surgery, Massachusetts General Hospital.

fields to care for the victims of various diseases. Our Greater Boston Community Fund has about forty of these on their list for aid. In addition we are cognizant of the March of Dimes for poliomyelitis, the work of the Tuberculosis League, and the national campaigns for heart disease, diabetes and arthritis. The American people are so constituted that they not only recognize their obligation to their fellow men but also feel the satisfaction of service and the joy of giving.

Urban communities have naturally more nearly covered these problems than the rural districts have. It must not be overlooked, however, that such agencies as the Commonwealth Fund, with its direction toward hospital service and medical education, have demonstrated the possibilities along these lines. The Bingham Associates, in conjunction with Tufts College Medical School, have proved the value of their service to rural areas in New England.* The frontier nursing established by Mrs. Breckenridge in the mountains of Kentucky is familiar to most of us here in Boston. There are doubtless many other voluntary organizations functioning in various districts that are less well known to us.

THE PRESENT SITUATION

The results of our present efforts are well illustrated by the report of Dr. Louis I. Dublin,¹ Second vice-president and statistician of the Metropolitan Life Insurance Company, who states

the American people never were healthier than in 1948, and the prospect is for continued improvement in 1949. The 1948 death rate will establish a new low in our country with a figure of slightly below 10 per 1000 population. This unprecedented record was achieved despite changes in our population structure, such as a large increase in the number of infants and a rise in the proportion of old people, both of which tend to increase the total death rate. Mortality rates in 1948 fell at every age period of life. The death rate from many important diseases touched new low levels, tuberculosis outstanding. In 1948 this disease will be down almost to 30 per 100,000, a reduction of about 40 per cent in the last ten years. The death rate from pneumonia was about 10 per cent under the previous low in 1947, owing largely to the ever-increasing use of sulfa drugs and penicillin. Infant and child health have achieved a splendid record, and mortality in infancy and childhood were at record-breaking low levels. Death of mothers in childbirth continued to decline. The mortality registered for chronic diseases of the heart, cancer and diabetes presented a different picture but show little change in the aggregate of the 1947 figure.

A further illustration is furnished by the following quotation:

Out of 1000 live babies born, one-quarter, or 250 babies, were doomed to death before attaining age 24 under the mortality conditions of 1900-02. The comparable age is now 59, with the majority of surviving persons, of course, living a good many years longer. This improvement is nothing short of amazing. Think of it: Three-quarters of the rising generation, the vast bulk of our new citizens, have a minimum longevity expectation now nearly $2\frac{1}{2}$

times greater than was the case a scant half century ago. And this statement does not allow for the further improvements which will be achieved, if present trends continue, during the lifetime of these new citizens.²

THE PROBLEM

The indigent have for many years received good medical care. This is accomplished through various tax-supported measures at the local level and by various philanthropic agencies including the voluntary hospitals. It has been the part played in this type of care by the voluntary hospitals that has resulted in the almost insurmountable deficits with which these institutions are now struggling. With the high tax rates it becomes more difficult for public-minded and generous citizens to meet the needs. The cost of medical care has been more than doubled in the past few years. Wages of all hospital personnel except doctors have been increased, and the hours of work shortened. Although it may be proved statistically that a dollar today will buy what 50 cents would have bought before World War II, it certainly does not work out that way as far as hospital care of patients is concerned. One of the great needs at present is to arrange for some adequate source to cover the actual cost of the care of the indigent patient.

The well-to-do also get adequate medical care. They can afford the physician of their choice and pay the specialist or consultant a regular fee. They can also meet the increased costs of hospital and nursing care.

There is a large percentage of the population who earn enough for the needs of themselves and their families until a major illness intervenes. These people form the backbone of our industry and are the ones who must have a plan whereby they can feel independent and meet the crisis of illness without either resorting to charity, which they abhor, or running into bankruptcy.

A survey prepared for and released by the American Life Convention, American Mutual Alliance, Association of Casualty and Surety Companies, Bureau of Accident and Health Underwriters, Health and Accident Underwriters Conference, Life Insurance Association of America, Life Insurance Conference and the National Fraternal Congress of America shows that more than a third of the nation is protected by some form of voluntary hospital insurance. Voluntary insurance plans for surgical and medical expenses cover approximately 26,000,000 persons. Newer types of protection account for an estimated 9,000,000 persons. Under the benefits for loss of income due to disability, 31,000,000 persons are protected. This represents more than half the employed civilians in the country. The number of persons covered under group insurance policies and under Blue Cross plans is 56 per cent greater than that at the end of 1945 and 241 per cent greater than that at the end of 1941.

*The recently developed Nashoba health center in Townsend, Massachusetts, is an excellent illustration of the voluntary solution to the health problem. This unit, built in co-operation by five surrounding communities, is a matter of local pride, and may well be used as a standard pattern for areas throughout the United States.

The carriers insuring against hospitalization expenses include insurance companies and fraternal societies, with an estimated 21,000,000 covered. Blue Cross Plans account for 28,000,000 persons.

In Massachusetts these insurance plans cover 60 per cent of the population. Blue Cross alone protects 2,000,000 of the 4,500,000 people in this state. Blue Shield in Massachusetts covers 750,000 persons.

The rapid growth of these voluntary plans throughout the nation is evidence that a high percentage of our citizens are self-respecting, independent-minded people. It could well be estimated that these voluntary plans will within a few years take care of the majority. I think we should give this a more adequate trial since the growth of such measures has been so spectacular.

Under these plans Dr. Paul R. Hawley,⁴ chief of the Blue Cross and Blue Shield Commission, says

the quality of medical care now being furnished in the United States is highly satisfactory. The quantity of medical care available leaves something to be desired, especially in the matter of more hospital beds and more nurses in every community and more physicians in many rural areas. The cost of good medical care is a matter of concern to many people.

WHAT IS BEING DONE

The Voorhees Subcommittee of the Hoover Commission has pointed out that there is a considerable amount of duplication and overlapping of effort in the Government-controlled medical services. It is heartening to learn that cognizance of this study is already taking effect. Early in January, 1949 the following information was released:

Secretary of Defense Forrestal made public the most detailed list of recommendations yet submitted by the Hawley Board, coincident with the first meeting of the new civilian advisory group which will succeed that board. The report, which Forrestal emphasized, has not yet received his approval, calls for decommissioning of two Army and one Navy general hospital, reductions of three Army general hospitals to station status and of 48 Army station hospitals to dispensaries, joint staffing of military medical installations that are used in common by personnel of Army, Navy and Air Force, joint utilization of specialists and consultants, establishment and joint staffing of specialty centers — tuberculosis and neuropsychiatry, for example. Signers of the 75-page report were Dr. Paul R. Hawley, chairman, Surgeons General Raymond W. Bliss (Army) and Clifford A. Swanson (Navy), Air Surgeon Malcolm C. Grow and Rear Adm. Joel T. Boone, executive secretary of the board.⁵

We now have more doctors per capita (1.710) than any nation in the world except Jewish Palestine, which is admittedly a temporary situation. It is true that the doctors are not evenly distributed, and there tends to be concentration in cities and in states regarded as having more pleasant climatic conditions. We may find that arrangements can be made to obtain a better distribution and thereby better service to those areas that need it. The statement so often made that we need more doctors requires further study. Perhaps we do, and if so something can be done about it.

That we do have a shortage of nurses seems apparent to all. When we take into consideration that the first graduate nurse, Linda Richards, received her diploma from the New England Hospital for Women and Children in Boston only seventy-five years ago it really seems miraculous that we are as well off as we are. Efforts are being made and plans are in operation to supplement the trained nurse with one of less training to carry much of the load. This major problem in the care of the sick will, I am sure, adjust itself into a much more rational and logical plan of nursing care than we have had in the past.

We have been agreeably impressed with the functioning of the Veterans Administration. Under the guidance of Dr. Hawley and Dr. Magnuson the American veterans receive better medical care than any other group of people. This was brought about by the selection of the staff doctors of Veterans Administration hospitals by so-called dean's committees. Full-time heads of services are well trained men. To help them, there are as many part-time consultants as are needed. These men are from the teaching institutions and bring all the new, tried and tested products of the research laboratories and medical clinics of the community to the veteran. There is no opportunity under such a system to subject these patients to obsolete methods or political rackets.

It is necessary for us to explore completely the medical needs of the nation. Each state must make its own survey. What is lacking in Massachusetts will probably be quite different from the shortcomings in Mississippi. Having done this in a careful manner, we should find ways and means of correcting the deficiencies.

On the basis of the experience of the Veterans Administration, I believe that a health plan for the nation could be evolved that would completely take care of the situation. This must vary according to the needs of the locale. Perhaps the most important problem is public health in a broad sense. This may be interpreted as including diagnostic facilities. In many places the facilities are already available, including existing hospitals both voluntary and Government controlled. In many areas the Veterans Administration hospitals already existing and those in the process of construction could serve. In some areas special diagnostic centers will need to be built. It would be possible in isolated areas for special diagnostic features to utilize mobile units.

These diagnostic centers should be under local and state control and the staff approved by the medical schools or, in states where no medical school exists, by the universities. It should be made possible for any citizen to avail himself of this diagnostic clinic. If he can afford to pay he should do so. If he has hospital insurance this should be taken into account. If he is indigent his services

should be paid for on a prearranged schedule by the community — a part by the local taxpayers, a part by the state and a part by philanthropy, the deficit under such a plan being borne by federal taxation

This, some of us think, would work, and it would assure the best medical service available in the country and would not be hampered by politics. It would cost something, but it would cost a great deal less than any federal-controlled, compulsory scheme that has been suggested, and it would not inter-

fere with the system of free enterprise on which this nation was founded and on which it has grown to be the greatest nation in the world

266 Beacon Street

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MEDICAL PROGRESS

PSYCHOSURGERY

MILTON GREENBLATT, M D,* AND PAUL GRAVES MYERSON, M D†

BOSTON

AN EDITORIAL¹ in 1940 referred to "radically wrong," "meddlesome surgery," which was a "violation of the Hippocratic oath." An opposing view was expressed by Fiamberri² "In the present state of affairs, if some are critical about lack of caution in therapy, it is on the other hand deplorable and inexcusable to remain apathetic, with folded hands, content with learned lucubrations upon symptomatologic minutiae or upon psychopathic curiosities, or, even worse, not even doing that." The first opinion is written by a man who fears an indiscriminate cutting of lobes and hemispheres by unconscionable surgeons, and the second by one who is motivated by the depressing picture of the hopeless, deteriorated, backward schizophrenic patient. Strong opinion and emotional bias continue to becloud the issue of psychosurgery.

The earliest psychosurgery is accredited to G Burckhardt, superintendent of a mental hospital in Switzerland, who, in 1890, operated upon the brains of 6 disturbed psychotic patients. There was 1 postoperative death, 1 recovery and at least 2 postoperative convulsive complications. But Burckhardt was impressed with the possibilities of this method.

At the International Neurological Congress held in London in 1935, Fulton and Jacobsen³ reported briefly on behavioral changes that developed in 2 chimpanzees after bilateral ablation of the frontal association areas. Stimulated by this report, Egas Moniz,^{3,4} in 1936, introduced bilateral prefrontal lobotomy in man.

*Instructor in psychiatry, Harvard Medical School; chief of laboratories and research, Boston Psychopathic Hospital; senior physician, Massachusetts Department of Mental Health; attending specialist, Mental Hygiene Division, Veterans Administration.

†Assistant professor in psychiatry, Tufts College Medical School; instructor in psychiatry, Harvard Medical School; physician-in-charge, Department of Nervous and Mental Diseases, Boston Dispensary; associate in psychiatry, Beth Israel Hospital.

TYPES OF PROCEDURES

Bilateral Lobotomy (Leukotomy)

Moniz and the neurosurgeon Lima first tried injection of alcohol into the frontal association areas and later invented a leukotome, a trocar-like instrument from the end of which a wire loop or a cutting edge could be protruded. Rotation of this loop within the frontal lobes cut cores in the white matter. Moniz made a superior approach on either side, 3.0 cm from the midline, and 1.5 cm anterior to a vertical line passing through the base of the tragus. He advised cutting four to six cores in each frontal lobe located at various subcortical levels. Among the complications encountered were sphincter disturbances, sluggish pupils and anisocoria. He also called attention to transient apathy, loss of initiative and disorientation, and said that there were "no grave repercussions in the part of intelligence or memory." Moniz stated that a third of his patients recovered, a third improved, and a third were not benefited. His best results were in agitated depressions, and his poorest results were in chronic schizophrenia.⁴

The Moniz technic has been modified, wholly or in part, by many surgeons. In America, the first lobotomies for mental disease were done in 1936 by Freeman and Watts, who became the chief proponents of psychosurgery in this part of the world. Their experiences with over 500 lobotomy cases have been summarized in a series of publications,⁵⁻²⁸ including a scholarly and interesting book, based on the first 80 cases, written in 1942.²⁹

Freeman and Watts have used a lateral or temporal approach entering at a point 3 cm behind the outer canthus and 6 cm above the zygoma. A blunt knife is introduced, with proper precautions

against too deep an entry, and the white matter in each frontal lobe is then severed along the coronal plane. Freeman and Watts have emphasized careful localization of the point of entry and adjustment of the plane of section in relation to clinical requirements. Deviation of the plane of section by as little as 5 mm may spell the difference between success and failure.²² Their standard operation has been used in 63 per cent of their cases, a radical or more posteriorly placed section in 37 per cent, and two or more operations in 12 per cent.^{9, 26} More anteriorly placed sections are employed in affective disorders, and more posteriorly placed sections in the schizophrenic disorders. Reoperations are usually done in a more posterior plane. The more anterior the incision, the less alteration in the patient's behavior, and the more posterior the incision, the greater the likelihood of interfering with area 6, with subsequent prolonged incontinence, convulsive seizures or transitory Babinski and grasping reflexes.¹⁵ Although the location of the plane of section is doubtless important, Mettler and Rowland,³⁰ on the basis of post-mortem studies, have pointed out that even when the Freeman and Watts lobotomy point is carefully defined on the skull, there is significant variation in the location at which the leukotome is inserted into the brain.

Yahn^{31, 32} has recently reported on 209 cases, 161 of which were operated on by the Moniz method and 48 by the Freeman and Watts method, but unfortunately for this comparison many of the latter were previously operated on by the Moniz technic. Yahn believed that superior results were not necessarily to be expected from the more extensive cutting in the Freeman and Watts technic. Although his results are not conclusive, the work represents one of the few attempts to compare different procedures in a single clinic.

Another noteworthy modification of the psychosurgical procedures has been developed by McGregor and Crumie³³ in England, where there is considerable enthusiasm for the surgical treatment of serious mental disorders.³⁴ McGregor and Crumie have devised an instrument with a rotating blade that is introduced 3 cm behind the eye and 5 cm above the zygoma and cuts a core 3 cm in diameter in the center of the lobe, in the coronal plane. The Great Britain Board of Control,³⁴ which in 1947 reviewed 1000 cases submitted to psychosurgery in various English centers, stated that there was little uniformity in the neurosurgical method used in that country.

Ström-Olsen and his associates,³⁵ in 1943, used both the Crumie technic and the method of Freeman and Watts, separately and combined, in 30 chronic cases with no hope of recovery by other methods and arrived at the conclusion that the Freeman-Watts procedure should be used in long-standing psychotic conditions, and the Crumie technic in the less severe cases.

In June, 1937, Lyster³⁶ did the first "open" operation. Approaching each frontal lobe superiorly, he turned a rectangular osteoplastic flap and with the aid of a specially lighted speculum attempted to separate the white fibers under direct vision. Lyster took pains to separate particularly the inferior frontal fibers because they connect frontal lobes with thalamus and hypothalamus—areas that are believed to have an exceptional role in the regulation of emotion and states of tension. Perhaps the chief exponent of the Lyster technic is J. L. Poppen, who with his associates has performed over 500 lobotomies by this method since 1943. Poppen³⁷ has introduced minor modifications of his own but adheres to the principles of superior approach, direct visualization of everything that is done and strict attention to fibers in the inferior or orbital aspects of the frontal lobes. The proponents of the "open" method believe that hemorrhage can be more successfully avoided by this technic, that it is possible to localize more accurately the plane of section in relation to cerebral structures, and to estimate more reliably the percentage of white fibers cut in that plane.^{37, 38} Statistics presented before the International Conference in Psychosurgery in 1948³⁹ indicate that the mortality is higher in the "closed" than in the "open" method. A recent poll of neurosurgeons in this country⁴⁰ reveals a preference here for the open technic, in foreign centers "closed" methods still prevail. No superiority for either procedure has been claimed in relation to postoperative seizures.

Unilateral Lobotomy

At a panel discussion in 1941, Lyster⁴¹ reported that he had done unilateral lobotomies in 4 cases, with good psychiatric results. The change was not so striking as when the operation was done on both sides, but a good unilateral operation might be as good as a partial bilateral operation. Freeman and Watts,²⁹ however, on the basis of their experience, concluded that both lobes must be operated on to obtain good results. Gavle and Neale⁴² and Van Waganen⁴³ also had unsatisfactory results with unilateral lobotomy.

On the other hand, there are data to suggest that unilateral lobotomy cannot be considered therapeutically worthless. Schwarz⁴⁴ performed a therapeutically successful unilateral lobotomy in a patient with a long history of a depressive state that showed a potentiality to remit after electroconvulsive treatment. Meyer and Beck⁴⁵ noted a case that showed considerable clinical improvement after a unilateral leukotomy.

Scarff⁴⁶ reported 10 cases in which ipsilateral, contralateral or bilateral pain was treated by unilateral lobotomy. The results were good in 7 cases. There was suggestive evidence that pain was more successfully relieved if the ipsilateral dominant

lobe were cut than if the contralateral nondominant lobe were cut. Curiously, 2 patients with bilateral pain were relieved by a one-sided operation. The results of the Boston Psychopathic Hospital group⁴⁷⁻⁴⁸ on unilateral lobotomy certainly indicate that further study of this operation for mental disturbances or for chronic pain would be eminently worth while.

Bilateral Orbital Leukotomy

Much thoughtful consideration has been given to avoiding unnecessary sacrifice of brain tissue. Some workers have been particularly impressed with an array of observations that have pointed up the special significance of the inferior or orbital aspects of the frontal lobes in determination of the personality. When Freeman⁴⁹ first experimented with the coring method of Moniz, he observed that "cores in the lower part of the frontal lobes produced a higher incidence of good results than cores placed in the upper part of each frontal lobe." Dax and Radley Smith,⁵⁰⁻⁵² using the McGregor-Crumbie leukotome and with a temporally oriented approach, carried out important studies of the comparative effects of leukotomies in various parts of the frontal lobes on separate series of cases. In 1946 they reported the results in patients who had received an "upper section," a "middle section," and a "lower section."⁵¹ In some cases horizontal sections were also made. These authors reported that depressions were most readily relieved by lower sections, aggressiveness of catatonic schizophrenia by an upper incision, and paranoid schizophrenia by a middle and horizontal section. In 1948 before the International Conference of Psychosurgery,⁵² they spoke of the desirability of the use of inferior or orbital sections in passive, apathetic depressions, in which the operation releases hyperactivity, euphoria and extroversion, and of superior or high sections, cutting fibers from areas 9 and 10, in cases with increased psychomotor activity. Additional middle and horizontal sections were used when more extensive leukotomy was desired.

In 1945, Hofstatter, Smolik and Busch⁵³ reported on 30 cases in which they had sectioned only the inferior quadrants bilaterally, using the Freeman and Watts method. They described improvement in 3 cases with affective psychosis, 1 with obsessive-compulsive neurosis, a decrease in somatic complaints in neurasthenia and significant improvement in various types of schizophrenia.

In two recent reports, Reitman⁵⁴⁻⁵⁵ further analyzed the cases operated upon by Radley Smith and stressed that the postoperative adjustment of patients who had received the orbital cut was superior to those with sections located elsewhere. Concerning the orbital cut, patients showing shallow affect, introversion, depersonalization or lack of initiative responded better than those suffering tension, anxiety, restlessness or aggression. Sym-

toms such as euphoria, overactivity and extroversion (often coupled with aggressiveness) were most likely to follow the orbital leukotomy.

Frontal Lobectomy (Unilateral and Bilateral)

Frontal lobectomy, prior to the advent of psychosurgery, was done only for serious disease in the frontal areas — tumors, epileptogenic scars, chronic abscess, meningocerebral adhesions or brain-crushing injuries of the frontal lobes. Prefrontal lobectomy has been extended by Peyton, Noran and Miller⁵⁶ to the treatment of mental illness in the absence of gross intracranial disease. This method was chosen because it allowed direct visualization of the operative field, the plane of section could be determined by visible landmarks, and the field could be inspected against hematoma. Furthermore, cerebral tissue could be removed, weighed and examined microscopically, and no devitalized tissue was left behind. Fourteen cases were reported in February, 1948, including 3 of severe psychoneurosis and 11 of schizophrenia — all with hopeless prognosis and five years or more of hospitalization. One patient died of accidental ligation of the anterior cerebral artery. Sensorial clearing required ten days on the average. Convulsive seizures developed in 4 cases. No patient made a complete recovery, 2 were considered markedly improved, and 9 moderately improved. Psychometric tests were not quoted.

Transorbital Lobotomy (Bilateral)

Fiamberti² (1937) thrust a "trocar" through the orbital plate and then either injected 10 per cent formalin or cut cores in the white matter of the frontal lobes with the Moniz leukotome. Freeman²⁸ determined on cadavers that by this method openings in the orbital plate could be made well behind the frontal sinuses, lateral to the ethmoids and anterior to the attachment of ocular muscles. Openings into the base of the frontal lobes were 3 cm lateral to the longitudinal fissure and 2 cm behind the frontal pole. Fibers in the central portion of the frontal pole were severed anterior to the rostrum and insula. The anesthesia was achieved by two or three electric shocks.

Postoperatively, Freeman²⁸⁻⁵⁷ stated that the patients had little more disturbance than would be attributable to the electric shocks. Fatuous euphoria, bland indifference and purposeless activity, often seen after the standard lobotomy, were not observed, but striking relief from anxiety was experienced by the patients, as with the conventional lobotomy. Complications were observed in only 2 of 10 cases, and incontinence was seldom seen. A third of the schizophrenic patients and half the involutional patients responded favorably to operation combined with electric shock. None of the unfavorable personality defects noted after prefrontal lobotomy were observed after transorbital

lobotomy, therefore, Freeman has suggested considering this operation earlier in the course of serious mental disease

Jones and Shanklin⁵⁵ used the transorbital lobotomy in 41 chronic cases. Worthwhile results (good or fair) were obtained in 80 per cent of the group. There was marked relief of anxiety and inner turmoil. The patients were ambulatory shortly after the anesthesia had worn off. The only significant complications were orbital ecchymosis, enuresis (in 3 cases) and transient unilateral ptosis (in 1 case). The authors recommended transorbital lobotomy in patients refractory to electric-shock treatment for whom a major lobotomy was contraindicated.

Topectomy (Bilateral)

In March, 1948, the Columbia-Greystone Associates⁵⁹ announced that a study was in progress to determine the effects of bilateral removal of areas of frontal cortex upon chronic mental disease. This study was undertaken in an effort to treat patients by means of a relatively small and precise surgical lesion, and to avoid the undesirable personal defects that often accompanied conventional lobotomy. An attempt was made to control the study by simultaneous observation of matched cases in which the patients received sodium amytal and phlebotomy.⁶⁰ An open-bone-flap operative procedure was utilized, and the areas removed included in all cases the medial or parasagittal portion of the superior frontal gyrus, approximately the rostral third of the superior frontal gyrus and an adjacent portion of the middle frontal gyrus. In patients studied less than a year, Lewis⁶¹ reported almost specific reduction in psychotic anxiety, no impairment in intelligence, learning, memory or abstraction, and no deaths, convulsions, persisting incontinence or personality deficits. The percentage of paroles after four months among patients operated on was significantly higher than that among controls. Removal of Broca's area did not lead to aphasia, and removal of the premotor area resulted in no permanent loss of motor function. LeBeau⁶² has done topectomies in 10 cases of uncontrollable agitation. There were 3 postencephalitic cases, 2 manic-depressive cases, and 5 patients suffering from epileptic seizures. LeBeau observed no blunting of the personality or social initiative and no change in convulsive episodes. No deaths occurred in the group. He also removed areas 9, 10 and 46 bilaterally in 8 cases of intractable pain, with therapeutic benefit. LeBeau considers the results of bilateral topectomy as good as those of lobotomy, although the former operation is a major surgical procedure.

Thalamotomy (Bilateral)

A psychosurgical technic that has received considerable professional attention is thalamotomy. It was first described by Spiegel et al.^{63, 65} By stereo-

toxic methods they made small circumscribed lesions in subcortical areas, with only minimal injury to overlying cerebral structures. In the treatment of psychoses, it was necessary to make at least five lesions in each dorsomedial thalamic nucleus with destruction of approximately a seventh of the nucleus before appreciable results could be obtained. Eight patients were operated upon, with 1 death, and 4 were sufficiently improved to go home. The method can be used in the treatment of unbearable pain by combining lesions of the spinothalamic system in the midbrain with lesions of the dorsomedial nucleus of the thalamus (mesencephalothalamotomy). The procedure was also recommended for treatment of convulsive disorder of subcortical origin.

Cortical Undercutting (Bilateral)

This method was recommended by Scoville⁶⁶ as a substitute for psychosurgery of the ablation type, which generally requires several tedious hours and large cranioplastic bone flaps. Scoville's operation is done in one hour, requires two trephine openings and produces little bleeding. The areas selected have been areas 9 and 10 of Brodmann (because of the success reported by others in ablation or leukotomy of these areas) and the orbital and cingulate areas because of their known influence on the autonomic nervous system and personality of animals. Undercutting of the posterior orbital surface (areas 13 and 47 of Brodmann) has not produced the sham rage and maniacal behavior reported in animal ablations of these areas.

The psychiatric and therapeutic results of this operation are not as yet available.

Bilateral Medial Lobotomy (Bimedial Lobotomy)

In 1945 Smith⁶⁷ showed that the anterior cingulate gyrus when stimulated produced autonomic effects — dilatation of the pupils, piloerection and cardiovascular and respiratory changes. Smith ablated the anterior cingulate gyrus (area 24) in monkeys and observed they became unusually tame and easy to handle, and Ward⁶⁸ noted that the animals lost shyness, fear of man, hostility and "social conscience." Ward suggested that psychotic patients might be benefited by an operation restricted to the cingulate area, a more radical lobotomy being thus avoided.

These considerations among others prompted workers at the Boston Psychopathic Hospital⁶⁹ to observe a series of cases in which the medial aspects of both prefrontal lobes were sectioned in an "open operation," using the superior approach of Lyster and Poppen. Particular effort was directed toward sectioning of the white matter related to the anterior cingulate gyrus on either side. Thus far the results in 14 cases followed four to six months indicate that the bimedial operation is therapeutically efficacious. Five patients were significantly

improved, 4 of whom were discharged home. Many symptoms characteristic of patients who received a full bilateral lobotomy were also found in patients who received bimedial or unilateral lobotomy — for example, weight gain, increased appetite, outspokenness and reduction in activity level.

Anatomic Considerations

The great variability of lesions produced by psychosurgery has been stressed by Dax et al.,⁵¹ Meyer, Beck and McLardy⁷⁰ and Yakovlev.⁷² The plane of insertion of the leukotome and also the amount of hemorrhage varied considerably in the cases reported by Meyer and his co-workers. In some of their patients who recovered the lesions were surprisingly incomplete and circumscribed, and structures near the midline were not involved. In other cases, either considerable improvement followed unilateral leukotomy, or the damage to one frontal region was negligible. In one case the prefrontal lobes were not involved at all.

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Thus, a great portion of the frontal-lobe cortex may be regarded as a projection area, receiving the products of activity of the hypothalamus in the same way that the visual cortex is the projection area for retinal activities.

Theoretical Considerations

In developing the concept of the use of surgery in the treatment of mental disease, Moniz believed that in the abnormal personality, pathologic ideas dominated the patient's mind, becoming fixed by the functional grouping of certain cells in abnormal relations in the frontal areas, and that beneficial results could be wrought only by destroying these morbid constellations.

Freeman, at first, was impressed by the marked reduction of tension in lobotomized patients and particularly the diminution of affect that formerly attached to pathologic ideas. This in turn seemed to be the very basis of the new interest in the outside world and appeared to release energies formerly trapped within the morbid framework. The thalamus was seen as an important emotional center that provided the energy connected with pathologic ideas, and severance of connections between thalamus and frontal cortex was the necessary step to reduce the emotional charge of abnormal ideas or to "bleach" the affect attached to those ideas. According to Freeman, the patient is fundamentally overly concerned with himself, suffers from anxiety and tension as he sees himself in relation to other human beings and to society at large, after the operation self-consciousness is reduced, foresight and insight are diminished, and emotion, which is still present, attaches itself to external happenings rather than to inner experience. Thus, after lobotomy the hallucinated patient may still hear voices but is not bothered by them, and the patient with cancer and fear of death casually admits to pain but is no longer deeply concerned.

Recently, Freeman has stated that foresight and insight are no longer tenable as hypotheses to explain the function of the prefrontal lobes and has focused his emphasis upon consciousness of self in its manifold forms as the primary business of the frontal lobes.

A further hypothesis that has been advanced tries to relate the function of the frontal lobe to the structure of modern dynamic psychology. According to this theory, damage to the prefrontal areas impairs the patient's "ability to perceive threats to his ego-organization." Since his formerly

marked defensive reactions are no longer called into action, he is freed from maladaptive behavior

INDICATIONS AND RESULTS

Lobotomy has generally been considered a procedure of last resort²³ Consequently, the patients, particularly in the early stages of its use represented hopeless and chronic forms of mental disease, for the most part relegated to custodial care Some of them were particularly disturbed persons who, because of hyperkinetic syndromes and suicidal or homicidal impulses, were troublesome problems of management to hospital administrators^{74 75} The follow-up studies of this material have helped to sharpen the indications somewhat, but large clinics have not departed from the use of the operation as a last resort, doubtless because irreversible brain destruction is implicit in this form of treatment.

Freeman and Watts²⁴ offer the opinion that results of prefrontal lobotomy are slightly better in females, Jews and Negroes Better results have been reported for mental disease of short duration than for disease of long duration, but, especially in the affective disorders (manic-depressive and involutional psychosis), duration of illness is not so important as clinical picture, degree of tension and so forth Patients with higher education are likely to make better postoperative adjustments than those with meager educational possibilities

From the point of view of nosology, lobotomy is first indicated in the affective psychoses (involutional psychosis and manic-depressive psychosis) that have been disabling for long periods and refractory to electric-shock treatment In manic-depressive psychosis when more than half the patient's lifetime is spent in the hospital, lobotomy should be seriously considered^{76 77} The results in the affective disorders have been encouraging, and many who would otherwise have been doomed to untold months of misery have been relieved of their suffering and reclaimed to some degree of useful living

Data gathered by Walker⁷⁸ from 12 authors indicated that of 150 patients with affective disorders treated by psychosurgery 63 per cent made social recoveries, 19 per cent were markedly improved, 13 per cent showed little or no change, and 3 per cent died In 250 cases classified as manic-depressive collected by the Great Britain Board of Control,²⁴ 48 per cent of patients were considered recovered and 35 per cent improved Considering the lack of uniformity in surgical procedures and in methods of appraising results, the similarity of results from various centers is astonishing^{12 16 17 72-86} Satisfactory outcome is uniformly reported in a half to three fourths or more of the cases^{12 16 17 72-91}

Lobotomy has not been so successful in schizophrenia as in the conditions mentioned above

Insulin and convulsive-shock therapy are considered therapeutic prerequisites in schizophrenic patients prior to lobotomy provided that a significant possibility of improvement with these therapies exists⁷⁵ Patients with paranoid and catatonic schizophrenia usually fare better than those with simple or hebephrenic types The familiar factors that are recognized as favoring a more hopeful outcome—such as good prepsychotic personality adjustment,⁹⁵ sudden onset, a clinical picture featuring turmoil^{74 96} and depression,⁹⁴ remitting tendency and favorable, if temporary, response to convulsive therapy—also apply in shaping the prognosis of schizophrenic patients after lobotomy

Walker⁷⁸ collected information from 16 clinics indicating that of 298 schizophrenic patients who received lobotomy 17 per cent made social recoveries, 24 per cent were markedly improved, 59 per cent showed little or no change, and 0.7 per cent died The results collected by the Great Britain Board of Control²⁴ revealed that of 599 patients 16 per cent recovered and 63 per cent improved In most series, about a third of the cases of schizophrenia show good results^{15 17 31 32 51 52 54 74 75 79 90 97-115} Only Heilbrunn and Hietko¹¹⁶ were disappointed with their results in 11 adult patients with schizophrenia, and Freeman and Watts²¹ with their results in 11 cases of schizophrenia that had begun early in childhood

Considerable enthusiasm exists for the use of lobotomy in long-standing obsessive-tension-ruminative states that have been progressively disabling^{9 11 17 74 91 93 97 117 118} Of 29 patients with psychoneuroses primarily of this type studied by the Great Britain Board of Control²⁴ 7 per cent recovered and 59 per cent improved

Thorpe¹¹⁹ and Rizzatti¹²⁰ pointed out the value of lobotomy in severe behavior disorders associated with psychoses of chronic encephalitis

Lobotomy has been considered contraindicated for constitutional psychopathy associated with cruelty, aggression, irresponsibility²⁴ and antisocial habits^{121 122} Alcoholism is not improved by lobotomy and may be made worse²⁹ Organic deterioration from severe arteriosclerosis, senility, general paresis and so forth has been considered a contraindication by some authors (Frank¹²⁴) Myerson and Myerson⁵⁵ have reported good results in chronic depressive states in patients over sixty years of age, and point out that age in itself does not necessarily contraindicate lobotomy provided the clinical picture is a favorable one

Freeman and Watts^{15 19} noted that some patients who suffered from severe pain coupled with anxiety, depression, gloomy foreboding and fear of death were greatly relieved after lobotomy When the fear of future disability was allayed, pain was borne with equanimity The operation has been applied in pain of phantom limb, focal neuralgia, mucous colitis, crippling arthritis, anginoid syn-

improved, 4 of whom were discharged home. Many symptoms characteristic of patients who received a full bilateral lobotomy were also found in patients who received bimedial or unilateral lobotomy — for example, weight gain, increased appetite, outspokenness and reduction in activity level.

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there have casually mentioned that such cases are rare, without discussing them in detail.

Relapse Following Improvement

Four cases of relapse are mentioned by Dax and Radler-Smith¹² among 129 patients who received operation 8 of 100 by Parker¹³ and 4 of 100 by Frank.¹⁴ Details are inadequate.

STUDIES

Psychologic Studies

Hunt¹⁵ was the first to study cases of prefrontal lobotomy. Forty selected patients operated on by Freeman and Watts were observed before and three weeks or longer after operation. A large battery of tests being used. Hunt found no evidence that total intelligence was decreased. Speed of performance was slowed, but accuracy improved on the average. There were better attention, fewer peculiar responses and greater tendency toward objectivity. Some patients accomplished more work with less strain and fatigue.

Kisler^{12,13,15} studied Rorschach tests in 20 cases followed up to one year after lobotomy and found that the differences before and after lobotomy were not substantial. Improvement in performance of the Rorschach test and clinical improvement did not necessarily parallel each other. Organic signs were usually attributable to the psychotic process, and in general it was difficult to separate the psychotic, preoperative personality from the effects of the lobotomy.

Robinson¹⁷ studied 10 selected cases in which the patients received lobotomy against 10 control cases matched for diagnosis and Binet vocabulary score. Many tests were pressed into service. Some aimed specifically at suspected deficit areas. Again no impairment in general intelligence appeared.

Porteus and his colleagues^{18,19} found insignificant changes in I Q tests (Binet) but marked impairment in the maze test. The maze test is purported to measure planned initiative, foresight, executive ability, capacity to consider several possibilities at once while action is delayed and power to sustain attention.

Babcock¹⁴ carefully studied a case of anxiety neurosis before and after lobotomy, and her results were interesting because her subject lacked the gross psychotic personality disintegration of most of the other patients studied psychometrically. The patient was quicker after lobotomy but made more errors, had a shorter memory span, could not recall as much of what he learned, was slower at perception of new conditions and demonstrated poorer judgment.

Other psychometrists such as Van Waters,¹² Brody¹² and Atwell,¹⁴ agree that although personality changes may be grossly apparent, evidence of brain damage due to the lobotomy is not regularly

observed. Many of the supposed postoperative effects on performance may be related primarily to changes in attitude, and that there is often a tendency in the favorable case to recuperate from clinical losses.

Holstead and Cowan²⁰ is significant from the standpoint of failure to demonstrate brain damage in numerous cases of tests that proved highly differentiating in brain injury, lobectomy and anoxia. Milner²¹ reports an outstanding exception to the generally negative results of other writers. He used I Q tests. In 7 cases of bilateral frontal lobectomy and 8 of unilateral frontal lobectomy, he found a consistent drop in general intelligence measured on the Bellevue-Wechsler intelligence scale.

In general, it may be said that the psychologists have reaped a poor harvest so far as tests of general intelligence or brain damage are concerned. The many strikingly negative results in cases with gross frontal lobe destruction have pointed up the coarseness of the present psychologic instruments used for detecting brain damage. These studies have so demonstrated that lobotomy produces much less disruption of psychologic functions than lobectomy does.

Psychologic tests for personality changes have been more fruitful, on the whole, but as yet have brought forth little of definitive value in the realm of measurements of drive, of frustration response or of social dynamics.

Physiologic Changes After Lobotomy

During the operation, cold climatic extremities often become warm and moist, the blood pressure falls particularly after sectioning of the first quadrant and diffuse perspiration may occur. Nausea and vomiting are also frequently noted as the fibers in the second lobe are cut. Urinary incontinence may be noted directly after lobotomy—a complication most troublesome to nurses. Inadequate control of anal sphincters, on the other hand, rarely occurs. Soon after operation many patients show markedly increased appetite and gain in weight. For a few days after lobotomy the patient may be in bed in a drowsy-nergic state usually motionless but capable of brisk arousal by stimuli to which he may even appear hyper-reactive.^{15,20}

Everly had one hypertensive patient whose blood pressure fell to normal and remained normal. Freeman had 3 hypertensive patients who showed prolonged lowering of the blood pressure after lobotomy. Chapman and his associates¹⁴ have very carefully studied both normotensive and hypertensive patients before and after lobotomy and have described a lowering of blood pressure, greater in hypertensive than in normotensive persons with a gradual return to preoperative levels within three months. Statistical evaluation failed to reveal a significant difference in preoperative and post-

dromes, tabes, carcinoma,²⁵ and so forth Poppen³⁸ described the case of a hopeless drug addict who was bed ridden, emaciated, and in constant torture because of severe discomfort and pain in the left side of the head along the distribution of the fifth nerve — although it had been divided intracranially. After lobotomy this patient was marvelously improved, and no longer required morphine. Hawkes and Gotten¹²⁵ compared prefrontal lobotomy with cordotomy for relief of intractable pain associated with carcinoma. Cordotomy was followed by extreme weakness, bladder paralysis and often incomplete relief of pain. Lobotomy produced spectacular relief of pain and nullification of anxiety relative to the carcinoma, and, furthermore, no narcotics were required after lobotomy. Lobotomy was considered far superior to cordotomy in the relief of intractable pain.

Scarff¹⁶ has recently tried unilateral lobotomy for relief of pain with notable success. Dynes¹³ ¹²⁶ reported on both bilateral lobotomy and unilateral lobotomy in a series of cases of pain studied at the Lahey Clinic. Relief of suffering was accomplished by this operation. In general, patients with metastatic cancer were more greatly benefited than those who displayed an exaggerated pain response in the presence of long-standing emotional instability. No anxiety, fear or concern over impending death was manifested in cases of cancer. The results appear to establish this procedure as a definitely useful tool in selected cases in the fight against unbearable pain.

Several authors have stressed symptom traits or syndromes that correlate well with eventual outcome. For example, a good deal of emotional tension ("tortured self-concern") is considered a favorable sign. Excitement, resistiveness, stupor, destructiveness and combativeness are favorable in schizophrenia, whereas docility, vagueness and apathy are contraindications.¹⁵ Peters¹⁴⁷ analyzed statistically a large number of preoperative traits and came to the conclusion that a heightened activity level (restlessness, agitation, euphoria, excitement and so forth) was favorable to improved social adjustment after lobotomy. Particularly beneficial results have been claimed for excited psychotic patients with pulmonary tuberculosis, lobotomy apparently provides much needed physical and mental rest.

Taxing clinical judgment is the decision not only whom to lobotomize, but *when* to lobotomize. The operative risk, possible personality deficits and the disadvantages of delay must be weighed against the probabilities of obtaining comfort, more satisfactory social and economic adjustment and a place in the community.

Postoperative Confusion

Freeman and Watts believe that patients showing the best postoperative results are those who

are confused, dull and retarded for several days or weeks after the operation. Confusion following sectioning of the fourth and last quadrant is taken as a sign that a sufficient number of white fibers have been sectioned. Kisker,¹²⁸ Meyer⁷⁰ and Petersen,⁹⁸ however, have not found confusion to be a significant element in improvement, whereas Gayle and Fishburn⁹⁷ believe that there is a somewhat better outcome in cases with postoperative confusion and incontinence.

COMPLICATIONS OF LOBOTOMY

Among the physical and neurologic complications of prefrontal lobotomy, Freeman and Watts²⁹ list vomiting, sweating, blood-pressure change, borborygmus, coma, ocular changes, frontal ataxia, staggering, fainting spells, heart changes, intolerance to drugs and hemichorea — as symptoms that do not persist. Symptoms that may persist include increased appetite, masked facies, vesical incontinence, rectal incontinence, convulsions, Babinski sign, aphasia, reflex grasping and hemiplegia. Sphincter disturbances have been mentioned by Ström-Olsen³⁵ and Peyton et al.⁵⁶

Convulsive seizures, a significant operative complication, have been reported from many centers. Stevens and Mosovich¹⁰⁹ reported an incidence of 33 per cent among 30 cases. Peyton et al.,⁵⁶ using bilateral frontal lobectomy, reported 4 cases among 14 patients operated upon, and Watts and Freeman²⁶ an incidence of 12 per cent among 250 cases. At the Boston Psychopathic Hospital the incidence of postoperative seizure complication has been about 10 per cent in 500 cases.¹²⁹ The seizures are usually few in number, however, many seizures and status epilepticus have been observed. The onset varies between days and years after operation, the larger number develop seizures between three months and one year postoperatively.

Grand mal is the principal type of seizure recorded by Greenblatt and Levin¹³⁰; Jacksonian seizures and attacks of rigidity were observed in a few cases only. No petit mal or psychomotor attacks were noted.

Deaths

The reported mortality has ranged from 1 to 4 per cent in the larger series — somewhat higher in "closed" than in "open" operations. Cerebral hemorrhage is the prime cause of death, with meningitis, pneumonia, ligation of the anterior cerebral artery, cardiac failure and anesthetic sensitivity claiming occasional lives.

Deterioration

Perhaps because of the hopeless nature of most cases in which the operation was performed, patients considered worse after lobotomy were indeed rare. Eleven cases were mentioned out of 1000 collected by the Great Britain Board of Control³¹ and 8 out of 618 collected by Zeigler.¹³¹ Other au-

Affectivity Although disabling depression, anxiety, and agitation are relieved, the patients may pay for the relief — in bilateral lobotomy, with a more superficial or shallow affective life.¹⁵⁵ Buoyancy and euphoria may result, particularly from the orbital operation.⁵⁰ In addition, some patients display irritability and aggressiveness, and a sudden flaring up of temper may occur when they are frustrated, with just as sudden cooling down, after the explosion, the patient is usually incapable of keeping alive a grudge.

Sexual Behavior after Lobotomy

Sexual behavior in the majority of cases does not seem to undergo any great alteration, according to Freeman and Watts.¹⁵⁹ Postoperatively, inertia may reduce the tendency toward gratification, on the other hand, the suppression of restraining forces may lead to freer expression along sexual lines. Lack of self-depreciating ideas permits normal appetites to emerge. Thus, the sex adjustment of married partners may sometimes be improved, and in some cases there is a return of sex interest that has been dormant for months or years prior to operation. The attitude toward sex is more objective and matter-of-fact, the patient may be less modest, unabashed or frankly outspoken. Only a few cases of exaggerated sexuality are recorded by Freeman and Watts, and no cases of sexual perversion or socially offensive conduct. Hutton has seen no antisocial or amoral behavior. McKenzie and Proctor,⁹⁰ however, state that 25 per cent of their cases showed "hypersexuality" with return to normal in nine to eighteen months.

Levine and Albert¹⁶⁰ studied 40 co-operative patients who had improved clinically after lobotomy and were functioning in their own homes. In general a decrease in sexual drive and in degree of gratification in sexual experience was noted. The intensity of pleasure accompanying the sexual act was usually less. Interpretation of this phenomenon was difficult in view of the long duration of illness and hospitalization of some of the patients with either abstinence or lack of normal gratification during that period. The dream and fantasy life was apparently impoverished. In a few cases sexual activity was increased, and some patients who had previously been inhibited for long periods became sexually interested. Two patients were excessively demanding after operation, one was an elderly gentleman who weaned his wife because of his abnormal appetite and "staving" power, the other was a young unmarried man who before operation was an inhibited obsessive-compulsive, and who afterward indulged lustily in both sex and drink and boasted of his prowess. Levine and Albert were impressed with the fact that sexual behavior after operation was generally kept well within the patient's moral bounds.

REHABILITATION

Impressed with the hypothesis that after lobotomy there is a new opportunity to crystallize personality organization into a more wholesome pattern, many workers have stressed the importance of proper rehabilitation programs designed to promote the full growth potentialities of each patient after operation. The great difficulty has been selecting programs properly individualized for each patient.

Immaturity, child-like behavior, lack of initiative and procrastination^{9, 10} are traits that have to be dealt with during the rehabilitation period. Suggestibility, lack of emotional restraints, greater interest in environment and less resistance to socializing are traits that favor progress in rehabilitation.⁵⁹ The necessity of beginning the work of readaptation as soon after lobotomizing as possible is emphasized by Whitman,¹⁶¹ Ewald et al.,¹⁶² Farmer¹⁶³ and others. Prolonged convalescence in the hospital, where rehabilitation can be carefully managed, rather than early discharge to an unorganized environment is favored, particularly by the English group of workers (Frankl and Mayer-Gross¹⁶⁴ and Fleming⁵⁹). Early discharge to the family may be attempted only when the relatives are mature with wholesome attitudes toward the patient,^{24, 161, 165} and when adequate supervision can be exercised at all times. Families should be chosen as carefully as patients, according to Watts⁹, Fleming⁵⁹ asserts that rehabilitation and re-education are the most important part of the whole treatment program. Readjustment and reintegration of the lobotomized patient may continue for three to five years. The rehabilitation period is therefore extremely long by any ordinary standards, hence, both long-range and short-range planning programs become a necessity.

During the rehabilitation period electric-shock and insulin-shock therapy may be used with success, even though the patient may have failed to respond to these procedures prior to operation (Whitman¹⁶¹ Fernandes¹⁶⁶ and Schrader and Robinson¹⁶⁷). Schrader and Robinson¹⁶⁷ state that electric shocks given after lobotomy appear to shorten the period of recovery and augment favorable results. Freeman and Watts⁹ used electric-shock therapy after lobotomy, particularly when improvement was followed by relapse.

We are indebted to Charles Atwell, M.A. for his help in preparing the section on psychologic studies and to Mrs. Loretta Smith, librarian of the Boston Psychopathic Hospital, for assistance in compiling the references.

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operative blood-pressure levels when sufficient time was allowed for recovery from the traumatic effects of the operation

The cause of the increase in appetite and weight is not thoroughly understood. Some are inclined to attribute the phenomenon wholly or in part to loss of tension, increase in contentment and self-satisfaction—that is, removal of cephalic inhibitions to eating. Improvement of gastrointestinal function has also been invoked to explain the phenomenon, for indigestion, dyspepsia and peptic ulcer are generally relieved postoperatively.

The explanation of the phenomenon of urinary incontinence has received some attention. Generally the wetting is attributed to indifference, apathy and neglect. It is found more commonly in the disorganized, deteriorated patients than in those who are well preserved. Rinkel, Rosen and Levine¹⁵² have made important observations bearing on the mechanism of wetting. They have shown that after lobotomy the bladder is often contracted, and the capacity low.

Members of the Boston Psychopathic research group (Rinkel et al.¹⁵³⁻¹⁵⁵) have attempted to appraise the stability or instability of the autonomic nervous system by response of the adrenergic or cholinergic system to specific stimulation. After operation patients with chronic schizophrenia showed a more pronounced blood-pressure and pulse-pressure rise to intravenous administration of epinephrine than that before operation. The carotid-sinus reflex, too, appeared to be more responsive to stimulation, for cardiac slowing and asystoles were more common after operation than before. The data were taken to indicate that the autonomic nervous system was for a time released from higher control by lobotomy.

After operation the patient is frequently hyper-reactive to many stimuli, often shrinking back from physical contact. Nurses find it difficult to take rectal temperatures, give baths or change head dressings. Removal of sutures is often violently resisted, and a very exaggerated reaction may accompany a venipuncture that was preoperatively accepted as routine. This reaction tends to be worse if the patient is allowed to anticipate the pain or discomfort.

PERSONALITY CHANGES AFTER LOBOTOMY

Is there a lobotomy personality? Earlier in the history of psychosurgery it was feared that lobotomy would reduce the patient to vegetable status, however, experience has taught that although considerable alteration may occur in the individual pattern, the core of the personality remains much the same—usually, to paraphrase Moniz, “there are no grave repercussions” in the part of the personality. Furthermore, the total personality constellation may change to a more wholesome adaptive type in which disorganizing fears, obsessions,

anxieties and even delusions and hallucinations have been mitigated or lost.

Widening experience leads one to a profound respect for the heterogeneity of personality modifications resulting from lobotomy. Quite opposite personality changes may, for example, be affected in patients who before operation presented similar psychoses. In some persons aggression may be allayed by lobotomy, in others, aggression may be released by lobotomy—what transpires apparently depending upon how the frontal association areas served the patient in question.

Changes of personality after lobotomy may be discussed under the following headings:

Drive. This aspect of the personality is usually, but not always, represented as being reduced. Thus, various authors speak of a postlobotomy apathy,^{70 110} laziness,^{156 157} lack of initiative,^{70 82} loss of spontaneity,³⁵ indolence,¹⁰ lethargy, reduction of active reactions to passive ones¹¹¹ and somnolence, particularly in the immediate post-operative period. Ambition and goal-directed enterprise are often wanting, being replaced by contentment with a matter-of-fact, simplified existence.^{156 157} On the other hand, the drive may be taken out of suspicious, hostile and aggressive attitude, the delusional or distorted fantasy life of the patient may be gradually uncharged, or episodes of unbridled violence may be muffled, allowing the patient to be tolerated among his fellows. Some patients, quite contrary to the general run, after lobotomy take up life with renewed vigor and return to challenging occupations with diligence and industry.

Self-concern. Perhaps the most specific functions of the personality attacked by lobotomy are those that relate to anxious self-concern and uneasy self-preoccupations. Tension, agitation, obsessive brooding,⁸³ self-consciousness, shyness,¹²¹ and excessive reserve are reduced. The patient is often less sensitive to criticism, rebuke or scorn.

Outwardly directed behavior and social sense. The patient is usually more accessible, for his energies are no longer so closely tied up with himself. He may turn his attention more toward reality, take notice of external influences and conditions, behave more appropriately in the group, seek out and enjoy others and no longer actively retreat from social intercourse. In his social relations, however, he may lack tact and diplomacy, may be abrupt in manners and speech, speak his mind without concern for the remote possibilities of his actions and make quick decisions without the advantage of deliberation. However, antisocial or amoral behavior has not been a conspicuous problem among lobotomized patients, and behavior is usually well within the bounds of the patient's former moral code.

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DIFFERENTIAL DIAGNOSIS

Dr T DUCKETT JONES Since the age of twenty-one this case had been a problem of clear-cut, severe rheumatic heart disease. We have in a large follow-up group a reasonably large number of persons with severe heart disease, all of them with mitral stenosis who are blood spitters. They do not necessarily at the time have any evidence of pulmonary edema or any evidence of pulmonary infarction, but over a period of years at frequent intervals they spit blood. The great majority of them have no evidence of active rheumatic fever. Many of them have been studied both in the hospital and outside with regard to x-ray examination of the chest, white-cell count, sedimentation rate and electrocardiograms. They have always been essentially normal so far as anything indicative of active rheumatic fever is concerned. The actual basis for the blood spitting can be explained much more accurately by Dr Mallory, but I would assume it was on the basis of extensive changes in the pulmonary vessels, which have been mentioned by a number of observers in the past, particularly Parker and Weiss.¹

I am surprised that no mention is made of the left auricle in the x-ray examination, because I think he must have had mitral stenosis. What the two attacks of pneumonia mean, I do not know. Whether it was really lobar pneumonia or pneumococcal infection is questionable. The rheumatic patient, however, does have attacks of pneumonia at times and for some strange reason over a period of years has survived them quite well, even before the days of modern therapy.

Obviously, this man had real mitral stenosis. I do not know what the relation between the so-called grippe and his decreasing cardiac reserve was. I doubt very much if it meant that he had active rheumatic fever, although that is a possibility. The liver was palpable and tender on examination in the Out Patient Department — four years before his final admission, so that he is known to have had failure for a long time.

The calf pain, I think, is possibly the first evidence that this man may have had bacterial endocarditis, and I raise the question immediately whether or not he was having emboli. It is obvious that he was considered as a possible or probable case of bacterial endocarditis at the time of the hospital admission.

"The apical beat was maximal in the sixth interspace, 7 cm. to the left of the midsternal line." I would strongly question that measurement, because it is rather obvious that the patient had a very extensive cardiac hypertrophy and I believe that most sixth-interspace hearts are well out and not 7 cm.

The heart "had an irregular rhythm, with an apical rate of 96 and a radial rate of 80." I think

that indicates that he had definite fibrillation, which shot his rate up on partial digitalization, but I somewhat doubt this because his previous difficulty was too much digitalis. I assume that the presenting feature of a mitral diastolic murmur had disappeared with the onset of auricular fibrillation, it is customary but not 100 per cent so. There is nothing in the description of the murmurs to indicate aortic as well as mitral disease, but most patients with rheumatic heart disease, with an impulse in the sixth interspace, have some aortic as well as mitral disease. I therefore think that he also had some aortic disease, although the description of the murmurs is not sufficient to make that a definite diagnosis.

The enlargement of the liver is to be expected because he had obvious cardiac failure. The cause of the splenic enlargement will be mentioned later. Both liver and spleen were tender, which might mean that he had splenic infarcts, I am not sure. Engorged livers are usually tender. It is perfectly obvious that whoever examined him was thinking in terms of the leg veins as a possible source of his trouble — a pulmonary infarct that happened a day or two prior to admission.

The blood picture was probably on the side of infection.

I believe it is likely that these urinary findings were of more importance than the ordinary urinary findings that one sees in congestive heart failure — more of that later.

There was some concentration of the nitrogenous products, and, of course, the carbon dioxide was reduced by more than 50 per cent.

The first thing to decide now is whether or not he had bacterial endocarditis superimposed on his rheumatic heart disease. He lived only about five weeks after the tooth extraction, and yet apparently he had been in no very different status in the few months prior to that extraction. In addition, the short duration would make it necessary for the endocarditis to have been an acute process, and the course was not that of acute bacterial endocarditis — that is, a high, striking temperature, usually with chills, and a rapidly progressive septic course. There was no sepsis, no fever, no chills, and no bacteria, which is somewhat against bacterial endocarditis, and the course was short for a subacute process. He had no positive cultures, which is evidence against subacute bacterial endocarditis but does not necessarily rule it out. In addition, he had real mitral stenosis, and it is unusual to have bacterial endocarditis on a severely damaged valve. Of course he may have had mild aortic disease, and the bacterial vegetations may have been placed there. Since no note was made that confirms aortic-valve involvement, and since he did have severe rheumatic heart disease, with real mitral stenosis, and auricular fibrillation, I submit that he did not have bacterial endocarditis.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 35251

PRESENTATION OF CASE

A thirty-nine-year-old Russian-born man, a clerk, entered the hospital because of malaise and low-grade fever.

Twenty-six years before admission, at thirteen years of age, the patient had an attack of rheumatic fever for which he remained in bed for ten days. Twenty years before admission he had another attack of arthritis. He first noted dyspnea on strenuous exertion eighteen years before admission and occasionally he spat bloody material. In that year he had an episode of acute failure after swimming half a mile. Subsequent examination revealed an apical diastolic murmur, and on x-ray study the left ventricle was enlarged. He gradually restricted exercise and was comfortable except for occasional periods of hemoptysis, often, but not always, brought on by exertion. He had pneumonia twice and numerous upper respiratory infections. About nine years before admission while doing only light office work he complained of insomnia that was due mostly to dyspnea. He had a long-drawn-out, rumbling diastolic murmur at the apex, with a presystolic accent transmitted along the sternal border. Six years before admission the patient developed grippe and enteritis and thereafter had progressive muscular weakness that incapacitated him. Severe breathlessness, sometimes in attacks, and insomnia were prominent. The liver was palpable and tender. There was no ankle edema. The diastolic murmur was much louder. An electrocardiogram four years prior to admission showed auricular fibrillation with partial auriculoventricular block and a heart rate of 50. He had been taking digitalis and doses of ammonium chloride for several months. Following readjustment of the dosage of digitalis the muscular weakness disappeared, and the heart rate increased. He was able to work about twenty hours a week with infrequent exceptions from that time until the episode of fever. One month before admission the patient had a tooth extraction. He then developed malaise, anorexia, loose bowels and a temperature varying up to

100.6°F. These symptoms, in addition to marked weakness, persisted until admission. The chronic cough and dyspnea continued. Small amounts of white sputum were raised. In the three days preceding admission he had generalized aches and severe bilateral calf pain. An x-ray film taken outside the hospital the day before admission was said to have shown pulmonary infarction. Four blood cultures taken during the present illness were said to have been negative.

Physical examination showed an orthopneic and mildly cyanotic man breathing at a rate of 36 per minute. The neck veins were prominent. Over the right lower and middle lobes resonance was impaired, and voice and breath sounds were increased. Many crackling rales were present, and expansion on that side was limited. The apical beat was maximal in the sixth interspace 7 cm. to the left of the midsternal line. The heart was enlarged, the border of cardiac dullness extending to the right. It had an irregular rhythm, with an apical rate of 96 and a radial rate of 88. The first sound at the apex was very forceful. There were Grade II apical systolic and diastolic murmurs. The pulmonic second sound was greater than the aortic second sound. The abdomen was distended, and the spleen and liver were palpated 3 and 7 cm. respectively below the costal margins, both were tender. There was moderate edema of the ankles. The calves were tender. Homans's sign was negative.

The temperature was 100.5°F, and the blood pressure 136 systolic, 88 diastolic.

Examination of the blood disclosed a hemoglobin of 15.5 gm. and a white-cell count of 16,700, with 88 per cent neutrophils. The urine had a specific gravity of 1.018 and gave a +++ test for albumin; the sediment contained numerous hyaline and granular casts. An electrocardiogram revealed auricular fibrillation, with a ventricular rate of 110 to 120. There was moderate right-axis deviation, the ST segment sagged in Leads 2 and 3. A blood culture was negative. Injection of penicillin was started on the first day. The superficial femoral veins were ligated on the second hospital day. No clot was found. Over the course of several days there was a steady increase in the severity of the patient's illness. He became more cyanotic, the heart rate increased despite continued digitalis, and the pulsations became weaker. On the third hospital day the nonprotein nitrogen was 52 mg. per 100 cc. The temperature returned to normal. Slight jaundice appeared. By the seventh hospital day he was weak and restless. The icterus increased. The nonprotein nitrogen was 106 mg. per 100 cc., and the carbon dioxide 13.1 milliequiv. per liter. During the last twenty-four hours there was no urine output. The radial pulse and the blood pressure were unobtainable. The patient died on the eighth hospital day after being in coma twenty-four hours.

nature of the acute terminal episode. It was not glomerulonephritis. The kidneys showed only relatively mild tubular degeneration which I think can be adequately explained as secondary to the other findings.

The surprise of the autopsy was provided on the lungs. Both lower lobes and the middle lobe of the right were very firm and heavy and cut with the consistency of leather. Even the two upper lobes were distinctly fibrotic. We were still further surprised when the microscopical sections came through. This photomicrograph (Fig 1) shows one of the medium-sized pulmonary arteries. The lumen is almost completely occluded by thrombus. The media has been completely destroyed and appears as a black in the picture. Around the outside of the artery is an inflammatory infiltration consisting largely of lymphocytes. The small branches

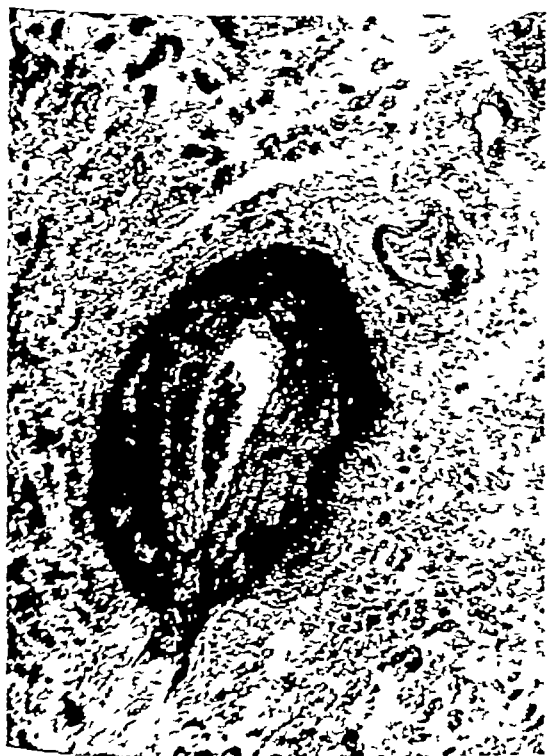


FIGURE 1

of the artery show the same picture: complete necrosis of the media, periarterial inflammation and thrombosis. The second slide (Fig 2) is an example of the fibrotic pulmonary tissue and could have been taken from any one of the three lobes. The lumens of the alveoli are lined with apparent epithelium. The alveolar walls are five to ten times as thick as normal, and the respiratory function must have been reduced by 75 per cent. The puzzling picture is that the pulmonary fibrosis

is old, whereas the arterial changes are for the most part quite recent. There are a certain number of vessels scattered throughout the lung that show newer changes. None of them impressed me as being more than a few months' duration. In contrast, the diffuse fibrosis is apparently a process of several years' duration tracing back, I should think, to one of the episodes of pneumonia. I would inter-

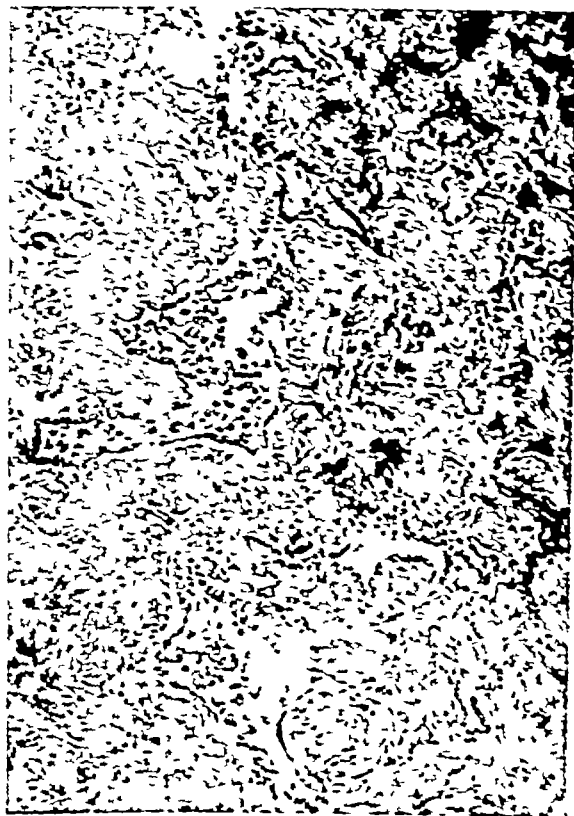


FIGURE 2.

pret them as organized pneumonia or pneumonitis. Another possibility is a healed interstitial pneumonia.

What are we going to call this? What are the arterial lesions? The histologic appearance of the individual lesion is essentially that seen in so-called periarteritis nodosa. On the other hand, many sections from all other organs in the body completely fail to show similar lesions. The vascular process was entirely restricted to the lung. The heart showed only completely healed endocarditis of the valves. There was no trace of activity in the myocardium. We have gradually become conscious in the last few years that periarteritis nodosa, so called, is not a specific disease but is simply a reaction pattern that can develop from a variety of etiologies. This case presents lesions anatomically entirely similar to periarteritis nodosa but limited to one

We have a great many things to explain on some other basis. What was the mechanism of the cardiac failure? Did he have sufficiently severe rheumatic heart disease to fail without any additional factor? We know that this occurs in adults. He had had failure off and on for eighteen years, so that I assume he had enough rheumatic heart disease to fail without very much in the way of active rheumatic fever. Also, I believe that he had kidney changes sufficient to cause some additional burden to the circulation. A good many patients with acute nephritis have heart failure, so that from the evidence it is possible that the nephritis had more effect on the terminal episode than actual rheumatic fever.

Did he have nephritis? He had retention of proteins. He also had jaundice. Do we have to make two diagnoses? Since rheumatic fever and glomerulonephritis can occur together and since they both have the same background of streptococcal infection, I am willing to believe that this man did have nephritis at the end, and that it played a definite role in his picture. I do not believe that bacterial endocarditis could be responsible for his nephritic picture. At least the patients that I have seen who died in uremia with bacterial endocarditis did so only after a long drawn-out illness.

We also have to explain the pulmonary picture. I suppose we should have looked at the x-ray films. We will come to them in a few minutes. I do not believe that we have to predicate the presence of thrombophlebitis in the legs to account for the pulmonary picture. Patients with failing rheumatic hearts often have pulmonary infarcts, but they can develop on the basis of disease in the pulmonary arteries rather than on the basis of embolism from the periphery of the body.

Did he have active rheumatic fever? Tooth extraction is known to stir up active rheumatic fever at times, and he did have a low-grade fever. He had an elevated white-cell count and had had at least two or three frank bouts of active rheumatic fever. If one exhaustively sectioned the heart muscle one might find Aschoff bodies or evidence of active rheumatic fever. However, it seems more likely that the additional nephritic burden, which I believe was present here, was sufficient to account for failure without an appreciable degree of active rheumatic fever. So I should like to guess that this man, who had severe rheumatic heart disease and mitral stenosis, also had glomerulonephritis, and that the severity of the rheumatic heart disease and the additional nephritic burden was sufficient to cause the entire syndrome that ended fatally.

Perhaps we should see the x-ray films.

DR JAMES R. LINGLEY: The heart shadow is grossly enlarged even though the film was taken with a portable apparatus at close distance. There is prominence to the right of the spine and marked prominence to the left in the region of the left

auricle. The pulmonary artery is enlarged, and there is some enlargement of the vessels throughout both lungs. In the left side there is a small quantity of fluid along the axillary border. On the right side there is a large, sharply defined shadow at the base, which in the lateral view is in the mid-chest, in the anterior portion of the lobe, and is consistent with infarct.

DR WALTER BAUER: Are we justified in making a diagnosis of glomerulonephritis without the presence of red cells in the urine?

DR JONES: We have only one analysis but he may have had red cells at another time.

DR BAUER: Jaundice occurs with pulmonary infarction, with congestive failure, perhaps the slight jaundice could be accounted for on that basis.

DR JONES: It has always been surprising to me that one does not get more jaundice in terminal rheumatic heart disease because the amount of liver change is tremendous.

DR BAUER: You would not be satisfied to say that the renal findings contributed by the laboratory studies could be adequately explained on the basis of congestive failure, phlebitis and pulmonary infarction?

DR JONES: I do not believe that as a rule the rheumatic patient develops uremia as a simple consequence of failure.

DR CHESTER M. JONES: In a few young persons we have seen definite jaundice without pulmonary infarction but with marked changes in the liver.

DR T. DUCKETT JONES: There have been three or four such cases. We have never been able to explain them other than on the basis of rheumatic fever causing liver change.

CLINICAL DIAGNOSES

Rheumatic heart disease, with mitral stenosis
Auricular fibrillation and congestive failure
Pulmonary infarction
Pneumonia

DR JONES'S DIAGNOSES

Rheumatic heart disease, with mitral stenosis
Glomerulonephritis
Pulmonary infarction

ANATOMICAL DIAGNOSES

Rheumatic heart disease, with mitral and aortic stenosis
Periarteritis nodosa of lungs
Organized pneumonitis
Hepatic cirrhosis

PATHOLOGICAL DISCUSSION

DR TRACY B. MALLORY: Autopsy showed, as Dr Jones predicted, very severe rheumatic heart disease. The mitral valve was reduced to a narrow slit, and the aortic valve was markedly stenotic. As he pointed out, the real question in the case was the

Examination of the urine was negative. The white-cell count was 23,850, with 87 per cent neutrophils, 3 per cent lymphocytes, 2 per cent monocytes, 1 per cent basophils and 7 per cent young forms. The granulocytes showed a shift to the right. The red-cell count was 8,260,000, and the hemoglobin was 18.5 gm per 100 cc, with a hematocrit of 76 per cent. The red cells demonstrated considerable variation in size and shape with some achromia, many cells showing polychromatophilia. The reticulocyte count was 7 per cent, with occasional normoblasts. The platelets were diminished. The sedimentation rate was 0. The bleeding time was 1.5 minutes and the clotting time 11 minutes. The prothrombin time was 5 per cent of normal. The plasma fibrinogen was 0.25 gm per 100 cc. A stool was soft brown and guaiac negative. The nonprotein nitrogen was 34 mg, and the total protein 6.2 gm per 100 cc, with an albumin-globulin ratio of 2.5, the serum calcium was 8 mg, the phosphorus 3.5 mg, and the alkaline phosphatase 5.9 units per 100 cc. The serum chloride was 102 milliequiv per liter. The van den Bergh reaction was 1.0 mg per 100 cc direct and 1.4 mg indirect. The cephalin-flocculation test was 1+ in forty-eight hours. The thymol flocculation test was negative. The thymol turbidity was 4.0 units. The bromsulfalein test showed 3 per cent retention of the dye in forty-five minutes. An electrocardiogram was defined as a normal tracing. The basal metabolic rates on two occasions were +69 and +59 per cent.

X-ray examination of the chest revealed some prominence of the cardiac shadow in the region of the left ventricle, with an elongated tortuous and partially calcified aorta. The lung fields were bright, with generalized prominence of the pulmonary markings. A plain film of the abdomen showed generalized decalcification of long structures, with collapse of a number of the ureteral segments. A large soft-tissue mass filled the left side of the abdomen and pelvis, with several flecked areas of calcification in the left pelvis. A dense linear streak of calcification in the left pelvis was thought to represent a calcified thrombus in the left iliac and femoral veins. Excretory urograms showed moderate embarrassment to drainage bilaterally but demonstrated no definite relation between the upper urinary tract and the abdominal mass. A barium enema revealed downward displacement of the major part of the colon by an extrinsic mass, but no intrinsic lesion was seen.

The patient was afebrile throughout the course of study in the hospital. On the seventh hospital day a sternal-bone-marrow aspiration was performed and reported as showing a myeloid-erythroid ratio of 9:1, with a marked shift of myeloid maturation to the right. No blast forms were seen, and there were rare promyelocytes. Megakaryocytes were plentiful. No plasma cells were seen. On the

fourteenth day a sternal-marrow biopsy was performed and marrow imprints were reported to show a myeloid-erythroid ratio of 6:1, with normal cells and increased megakaryocytes. On the following day the patient developed a painful subpectoral hematoma in the region of the biopsy site. Subsequently she complained of mild perspiration and chill sensations, with pleuritic pain over the right lower chest posterolaterally. There was no cough or hemoptysis, but there was slight tenderness in the left calf and thigh. On the seventeenth hospital day while elevating her arms for an x-ray examination of the chest, she experienced sudden pain in the left anterior chest and subsequently noticed rather rapid increase in size of the hematoma with extension over the chest and posteriorly. Subsequently she developed rather severe hypertension and a feeble pulse, with a radial rate of 130. Intravenous injection of protamine and intramuscular administration of vitamin K were given in addition to fluids intravenously and sedation. On the following day, the subpectoral hematoma was evacuated under local anesthesia. Postoperatively she had a pulse rate of 150, but the blood pressure was not obtainable. She was drowsy but responsive and coherent. There was no cyanosis.

On the nineteenth hospital day she developed dyspnea of progressive severity and abdominal distention with ileus and died quietly and abruptly the same evening.

DIFFERENTIAL DIAGNOSIS

DR. JOSEPH C. AUB: The description of the mass is important because the description of a tumor low in the abdomen suggests a tumor in the ovary, but there was no history of recent vaginal bleeding.

The chest findings mean nothing but congestion of the lungs, they do not imply fluid.

There are only three reasons for the slowed prothrombin time: a vitamin K deficiency, liver damage or the eating of red clover. There is no history of the eating of red clover, which is used as a treatment for cancer by traditional American folklore. Perhaps the patient was taking red-clover tea. The albumin-globulin ratio showed a relatively reduced globulin. The liver was large. The phosphatase was a little high. All this is hard to interpret but suggests diminished liver function.

It is interesting, but not exciting, that the basal metabolic rate was elevated because it may be quite high in both leukemia and polycythemia.

So far, I should say that this patient had polycythemia vera, because the white cells were mature. Why the platelets were diminished is not clear.

It will be very interesting to see if the x-ray films show a great deal of emphysema. This might account partially for the polycythemia, and I would like to find some reason for anoxia. It is interesting that in polycythemia, one gets decalcification of

organ in the body. It could be considered evidence of acute rheumatic infection, but we have no confirmation.

There was one additional finding of some interest. The liver showed a very well developed cirrhosis such as can occur in chronic rheumatic heart disease, but it seemed to me more marked than that ordinarily seen in this degree of mitral stenosis. The right ventricle was also unusually thick. It measured 1 cm. in thickness compared with a left ventricle of only 1 1/4 cm. I think that without much doubt the pulmonary lesion considerably increased the strain on the right ventricle, beyond what could be explained by the mitral involvement.

DR JONES: Would you think the pulmonary lesions, the acute ones, were comparable to Rich's² sulfonamide cases?

DR MALLORY: Yes, they are perfectly consistent with that.

DR JONES: I do not know whether this patient had sulfonamide prophylaxis at the time of death.

A PHYSICIAN: He did not develop signs of consolidation in the right lower lobe until two days before coming to the hospital.

DR MALLORY: We found nothing to explain that. All the lesions there are of years' duration.

DR JONES: Would you agree that these changes — if they are to be considered as evidence of active rheumatic fever — would call for a complete re-evaluation of what we term active rheumatic fever, on the basis of the findings that we see in the younger person? One does not find this pattern very often.

DR MALLORY: No, there are occasional cases of active rheumatic fever with arteritis so severe that one begins to think of calling it periarteritis nodosa, but these cases are the exception.

DR BAUER: Would the roentgenologist be able to read this chest plate differently now?

DR LINGLEY: I am afraid not. I do not understand what the shadow in the right lower lobe could be.

DR BAUER: Are you wholly satisfied with the explanation of the pulmonary changes?

DR MALLORY: As a healed pneumonitis?

DR BAUER: Yes.

DR MALLORY: I think there are two alternatives, either healed pneumonitis or the scars of long successions of pulmonary infarction. I am rather sure that one can rule out the latter.

CASE 35252

PRESENTATION OF CASE

A sixty-nine-year-old divorced woman was admitted with the complaint of an abdominal mass that had been increasing in size over a period of seven years.

When first detected it was said to have been the size of a walnut, located in the left lower quadrant and without associated symptoms. About three years before admission the mass had increased markedly in size and the patient began to notice increasing urinary frequency, nocturia and anorexia. At the same time she began to notice a tendency to bruise easily. She had some discomfort when erect, and difficulty in sleeping required medication from her physician. As the mass increased in size she developed moderate dyspnea and some palpitation on exertion, for which she was given daily green pills. At the time of admission, almost the entire abdominal cavity had become filled with the mass. She had lost 30 pounds during the previous three years but denied nausea, vomiting or change in bowel habits. There apparently had been no vaginal bleeding since the menopause at the age of fifty-three.

Twenty-nine years before admission she had an episode of post-partum phlebitis in the left leg and had recurring ulcerations about the left ankle. About twenty-five years before entry she had an episode of severe hemorrhage following multiple tooth extractions.

Physical examination revealed an emaciated, elderly woman with bronze pigmentation of exposed skin areas and multiple ecchymotic spots over the arms and upper trunk. Her color was high but not violaceous. A few telangiectases were present over both cheeks and the right ear. The heart was somewhat enlarged to percussion. There were frequent extrasystoles occurring irregularly and a Grade I, precordial systolic murmur. The aortic second sound was greater than the pulmonic. There was some dullness to percussion, and decreased breath sounds with fine crepitant rales at both lung bases. A large, smooth, hard mass filled almost the entire abdomen except for a portion of the right upper quadrant. It was not easily movable but was not attached to the abdominal wall. A definite notch was palpable on its right border below the level of the umbilicus. It was not palpable rectally, and the pelvic examination was within normal limits. The liver edge was palpable about four fingerbreadths beneath the costal margin in the right flank. A few small soft and nontender lymph nodes were palpable in the inguinal and cervical regions bilaterally. There was some distention of superficial veins in the neck and left leg. Slight edema, skin pigmentation and old scar formation were present about the left ankle.

The blood pressure was 148 systolic, 90 diastolic.

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the vertebrae, where a great deal of blood is made, and where the bone is composed largely of trabeculae that may become so thin that vertebral collapse may result

The x-ray findings establish the fact that this mass was the spleen and not the kidney. If it were kidney or a retroperitoneal mass, the large bowel would be pushed over and not pushed down by it. It is only the spleen that pushes the large bowel ahead of it.

The bone marrow contained an enormous number of white cells. Dr. Jacobson says the normal ratio is 4:1 to 8:1. Certainly, with polycythemia vera there should be many more red cells than white cells. This is a high number of white cells for polycythemia but does not rule it out. There were very few platelets in the circulating blood, and yet many megakaryocytes were present in the bone marrow. No plasma cells were seen. We must think of multiple myeloma, in spite of this fact and the normal total protein and low globulin in her blood, but it is unlikely.

The first part of this case is, I think, easy. The second part is very baffling. I do not know just where her pain started, whether this was a pulmonary infarct, or whether it was bleeding with irritation of the pleura. She had tenderness in the calf and thigh, and, I suppose, an embolus was liberated from the phlebitis of the leg.

There is little description of the x-ray examination done at this time — whether it showed evidence of bleeding in the pleura or in the pericardium.

Well, there it is. The mass was the spleen. The diagnosis is polycythemia vera. There are a good many questions in relation to that. Why did she have so few platelets? The blood of polycythemia ought to have many platelets. She had a great many megakaryocytes in the bone marrow but very few platelets in the blood stream. I do not know why. She bled, which is common in polycythemia, and I think she died of bleeding. She had a high white-cell count, 23,800, and all the cells were mature, with no abnormal cells, this is also common in polycythemia. In fact, I recently saw a patient with straight polycythemia who had almost 100,000 mature polymorphonuclear cells. About 10 per cent of patients with polycythemia have leukemia as they progress. But I do not believe that this patient had leukemia.

I see no good evidence for the diagnosis of agnogenic myeloid metaplasia. Incidentally, this disease interests me very much as a preneoplastic lesion. This disease is a beautiful example of an enormous, increased production of red cells. Why it causes an increased production of normal adult red cells and then ends up with a neoplasm is fascinating, there is no explanation for it that I know of, and it remains an interesting opportunity for the study of preneoplastic lesions.

I want to see the x-ray films.

DR. JOSEPH HANELIN: I believe she has an emphysematous chest. The anteroposterior chest diameter is increased, and the sternum bulges forward.

The first set of chest films, taken on the second hospital day, shows findings in the chest essentially as described. The heart is somewhat enlarged, and the left ventricular salient is prominent. There is calcification of the aorta. In the lateral film of the chest multiple vertebral fractures involving the lower thoracic and upper lumbar segments are visible. There also appears to be a rib fracture on the right. The left costophrenic sulcus is blunted. One wonders whether this might be due to underlying infarct or whether it is possibly of longer duration, owing to some thickening of the pleura.

On the sixteenth hospital day, the chest findings have changed slightly — at least, to demonstrate very nicely the large subcutaneous hematoma, which is now visible anterior to the sternum. I rather suspect that the density noted overlying the left portion of the thorax is also due to subcutaneous blood accumulation. There is a small amount of fluid in the right costophrenic sulcus, possibly related to the rib fracture.

The plain abdominal film confirms Dr. Aub's impression that he was dealing with an enlarged spleen. There is a large mass in the left abdomen of ovoid configuration. The normal splenic shadow cannot be seen. I assume this is an enlarged spleen. In addition, the lower edge of the liver is situated below its normal location and extends slightly below the iliac crest. Pyelograms show slight embarrassment to drainage on the right and a slightly hydronephrotic renal pelvis on this side. Renal function may be impaired somewhat bilaterally. In the abdominal film there is a calcified streak following the course of the left iliac and femoral vein, which probably represents a calcified thrombus. In the anteroposterior view, we can also note the fracture of the lumbar segments. All the bones are decalcified, but in a woman of this age, the degree of osteoporosis is not unusual.

DR. AUB: The emphysema does not help me because it is not sufficiently marked. I do not think this patient had kala-azar, or myeloid metaplasia. She had polycythemia, as I said before, and I think polycythemia vera. So far, I am sure that I am on firm ground. From here on, I am on less firm ground because I do not know whether the hemorrhage killed her, or an infarction. Patients with polycythemia have hemorrhages, — this patient had had hemorrhages for a long time, — and they bleed very heavily, just as patients with leukemia do. This patient also had few platelets and a slow prothrombin time. Also, in polycythemia thrombi develop, and they may get loose. This woman died in shock, and she died while she was bleeding. Therefore, it seems to me, she died of either hemorrhage or infarction. The sternal biopsy may have gone

through into the upper mediastinum, and may have extended into the pleura, and hemorrhage may have occurred in the pericardium with subsequent cardiac tamponade. I have not enough evidence to say whether these occurred. She had some suggestion of phlebitis in her leg. There is evidence of old phlebitis. She had a sudden sharp pain in the chest, though she did not cough or spit up blood. She may well have had a pulmonary infarct, sufficiently great to cause anoxia, shock and death. She may possibly have had a cardiac infarct.

I have not enough evidence to make a differential diagnosis. I have some evidence that she was bleeding and some evidence that she had cause for having a large pulmonary infarct, no evidence is given that she had a cardiac infarct. I know she was bleeding about the sternal biopsy, and these people do go into shock from hemorrhage, and I believe that she kept on bleeding, with extension into some cavity, either pleural or pericardial. I rather guess that she had a large pulmonary infarct from which she went into shock and died. Therefore, I should be surprised if she did not have polycythemia vera, and I do not expect myeloid metaplasia or neoplasm in the bones. Her thin bones were due to the fact that they were full of actively regenerating blood and that the trabeculae had been hollowed out by this long, slow disease. I think her large spleen was due to polycythemia. Then it is to be expected that the liver has areas of regeneration of red and polymorphonuclear cells, with some hemosiderin in her liver, and probably in her spleen.

DR BERNARD M JACOBSON: Is there any record of the red-cell count and the hemoglobin in the last few days of life?

DR DAVID G FREIMAN: Do you know, Dr Milam?

DR DANIEL F MILAM, JR: She had severe hemorrhage, on the following day the hemoglobin was 17.8 gm.

DR FRANCIS T HUNTER: I saw the patient for about two minutes before she was transferred to the surgical department for biopsy. I never saw her again. There was evidence at that time that she had an enormous spleen. Because of the immature white cells in the smear, I thought she might belong to the small group we have seen in the clinic that we cannot make up our minds whether to call polycythemia vera or leukemia with polycythemia. Those with enormous spleens have a relatively benign course, provided they are left alone. Some that we have treated have done very badly. The usual case has a white-cell count of 50,000 to 100,000, with myelocytes and myeloblasts and so forth in the smear. Speaking of polycythemia becoming leukemia, I know of one case of typical polycythemia vera that was treated with "spray" radiation and did well. But after ten years she entered the Baker Memorial with a white-cell count of 150,-

000, all myeloblasts, and promptly died. Another point that suggests that this case may have been more leukemic than polycythemic — although I admit that I cannot tell where one begins and one ends, or whether they are not one and the same disease — is that the basal metabolic rate was high. In polycythemia the basal metabolic rate is about +25 or +35 per cent, in leukemia it is +70 or 80 per cent. We must remember that this patient had a long history, and, having had no treatment, she could have developed this enormous spleen with polycythemia vera alone. One thing missing in the history is that there is no mention of how long she had the ruddy complexion. Had she been that way all her life?

In regard to the basal metabolic rate, a few days ago I had quite a surprise. At autopsy the patient's spleen was not enlarged but the liver was, and the peripheral blood showed many nucleated red cells and myelocytes. It was my opinion that the high basal metabolic rate (+40 per cent) was in favor of leukemia. Because he was going downhill so rapidly, he was given no x-ray treatment and died soon thereafter. Post-mortem examination showed complete replacement of all the organs with cancer of the prostate. I had not seen such a high metabolism from cancer before, and this was explained by the rapidly growing tumor cells.

As to death from hemorrhages in this case, there is one cavity not mentioned. How about the peritoneal cavity? Could she have had a ruptured spleen?

DR AUB: The basal metabolic rate varies with the number of young cells, and in this disease may be due to the high, specific dynamic action of protein. The red cells discard their nuclei, and the uric acid excretion is high, and so there is a high protein breakdown from this disease. Besides, the white cells that were present in this bone marrow could account for some of the high metabolic rate on the basis of rapid regeneration of cells. As far as having bled into the abdominal cavity is concerned, that is possible. I do not know where the hemorrhage gravitated to.

DR HUNTER: I mentioned that because there was a case of leukemia on the medical ward a good many years ago, the patient squeezed his abdomen hard, went into shock and died. He had ruptured his spleen just by pressing on it.

DR AUB: It is not unusual to have the white-cell count as high as this with polycythemia.

DR HUNTER: That is true.

DR JACOBSON: I recall asking the patient how long she had had a ruddy complexion. She did not recognize that she had any abnormal high color, and she did not know the answer to that question. The protocol gives no adequate picture of what she looked like. She was one of the most emaciated women that I have ever seen. In addition to the ruddy complexion, she presented a peculiar pigmentation that in the minds of some observers raised

the question of Addison's disease or similar rare conditions. If there is any diagnostic information to be obtained at all from the bone marrow, certainly, in her case, it was not leukemia. The shift was to the right. The white-cell elements were more mature than normal, not less mature, and that is what influenced me mostly in thinking that she was not leukemic, at least, not at that time. It is interesting that on the surgical service she was given intravenous protamine to stop the hemorrhage, with the idea that she had had heparin-like bodies circulating and causing hemorrhage. As I recall, in looking at one of the initial smears, I was not impressed with the diminution in platelets. I do not believe the bleeding was due to thrombocytopenia. I think that anyone who saw her in her fragile, emaciated condition would have been loath to do anything major in the line of surgery on her without some type of treatment directed toward the blood-forming organs.

CLINICAL DIAGNOSES

Polycythemia vera
Splenomegaly
Subpectoral hemorrhage

DR AUB'S DIAGNOSES

Polycythemia vera
Hematopoiesis of liver and spleen
Pulmonary infarct

ANATOMICAL DIAGNOSES

Polycythemia vera
Hematoma, massive, subpectoral and subcutaneous
Hematoma, slight, mediastinal
Splenomegaly, marked
Myeloid metaplasia, spleen and lymph nodes
Erythropoiesis, focal, liver and adrenal glands
Pyelonephritis, chronic
Thrombosis, left iliac and femoral veins

PATHOLOGICAL DISCUSSION

DR FREIMAN. At autopsy this patient was an emaciated woman with extensive ecchymosis over the anterior thorax, especially on the left, extending up over both shoulders into the neck, and down over the left flank and abdomen. A hematoma was

present over the sternum at the site of the sternal biopsy, and a stab wound was present in the anterior axillary line, where a massive subpectoral hematoma had been drained surgically. The subpectoral area contained a large hematoma. The body cavities contained no blood. Our approach was limited to an abdominal incision. When the peritoneal cavity was opened, a large spleen presented, extending to about the brim of the pelvis in the midline. It weighed 3050 gm. The liver was moderately enlarged, weighing 2300 gm. Microscopically, the spleen showed very active myeloid metaplasia, with excellent maturation of all elements and many mature forms. The sinusoids of the liver also revealed hematopoiesis, chiefly of erythroid elements. The sections of bone marrow that were examined showed intense hyperplasia replacing all the fat, here, too, there was excellent maturation in all series. Large numbers of megakaryocytes were present in the marrow and spleen. The lungs demonstrated some atelectasis and emphysema, but there was no evidence of embolism or infarction. The left kidney weighed about 100 and the right 170 gm., both kidneys showed fine granularity that was due to chronic pyelonephritis. In the pyramids of the kidneys there were white streaks, which proved on microscopical examination to be urates in the collecting tubules. This may be related to the fact, as Dr Aub pointed out, that patients with polycythemia excrete considerable amounts of uric acid, probably owing to excessive nucleoprotein breakdown in the course of active erythropoiesis. As a matter of fact, cases of gout or gouty exacerbations have been described in association with polycythemia. There was an old thrombosis extending into the left iliac and left femoral vein as far as we could reach — the residue of the old phlebitis.

DR AUB. Why did she go into shock?

DR FREIMAN. As far as we could tell, it was due to the massive bleeding into the subpectoral area. The only internal evidence of bleeding was a small hemorrhage in the posterior mediastinum.

DR AUB. It does not take much there.

DR FREIMAN. Perhaps, but it did not seem to be producing any occlusion or compression.

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MEDICAL CARE AND INDIVIDUAL INITIATIVE

ELSEWHERE in this issue of the *Journal* Drs McKittrick and Allen discuss the question whether the good of the American people demands compulsory health insurance. The opinions given and the conclusions drawn represent the physician's answer to those who advocate Government supervision and direction of medical practice. Interest in these papers is heightened by the fact that they were delivered before a lay audience.

Dr McKittrick takes up in detail the arguments invariably advanced by the proponents of federal health insurance, presenting in rebuttal the facts as they appear to the majority of doctors. He reconsiders the comments on the state of the nation's health—so often interpreted and misinterpreted as to offer obfuscation rather than enlightenment—in terms of whether they prove that the Govern-

ment's program is the only means of achieving the desideratum of the best possible medical care for the American patient. Thus, he finds no evidence that compulsory health insurance will improve the health of the nation, that it is necessary if medical services are to be furnished the 70,000,000 people who have difficulty in providing adequate minimal care for themselves and their families," or that it would meet the requirements of a good national program. He points out the danger that the proposed federal system would eliminate any possibility of experimentation outside the structure of the compulsory, centrally controlled plan" and he offers the opinion that such a program would eventually lower the quality of care received. Finally, he states that the history of medical progress gives promise that the problem can be solved without sacrifice of the initiative and freedom that have raised American medicine to its present eminent standard.

Dr Allen discusses the plan for better medical care in relation to what the profession has accomplished without the fetters and annoyances of federal dictation. He traces the progress in medical education, hospital standards and research that has made possible the present status of American health. He emphasizes the value of the system of free enterprise" that has helped progress in medicine and other fields. In forthright terms, he recommends a program that will provide medical care for those who cannot afford to pay for voluntary health insurance: community co-operation among local taxpayers, the state and philanthropy, with federal taxation to meet the deficit.

The proposals advanced in these papers appear to have merits that compulsory health insurance lacks. The argument in favor of Government medicine concentrates on the needs of people who cannot afford to pay for voluntary health insurance but ignores the contribution of private philanthropy and voluntary community and state agencies to the care of the medically indigent. It makes much of doing away with a means test (accepted with apparent unconcern by those who benefited from the WPA and work relief but now somehow intolerable to the free American, or to those who pretend to speak for him) in a way that, absurdly enough,

would provide free care for the wealthy ne'er-do-well along with his less fortunate fellows, the burden, presumably, would fall on the man with a job, the inevitable scapegoat in ill considered programs

The authors of the papers referred to are to be congratulated for their dispassionate but cogent presentation of the physician's side of the case. It should be evident to lay and medical readers alike that the physician's side is none other than that of the patient — the end in view is the good of the patient. It is high time the medical profession made its voice heard, not by its confreres but by the public, which in the final analysis will be the judge of what plan to accept or reject and what kind of medicine, Government or private, is best suited to its needs. The papers discussed offer assurance that the future health services of Americans can best be planned by those who provide the service

DAMAGED GOODS

THE careful study by Ingalls and Prindle of 107 cases of esophageal atresia with tracheoesophageal fistula, reported elsewhere in this issue of the *Journal*, suggests many still unexplored possibilities in the etiology and prevention of congenital defects. Most spectacular among recent revelations of applied embryology has been the incontestable sequence of events between maternal rubella and certain well known anomalies occurring in the fetus. Equally challenging are such anatomic variations as those of the trachea and esophagus, nonfamilial and obviously not hereditary, yet occurring with a degree of regularity that has made such an investigation imperative.

Studies on human embryos have shown that these specific defects are present long before birth—as early, in fact, as the second month of fetal life. The broad pattern of tracheoesophageal fistula, which indicates a departure from normal sequences of development occurring at about the fifth or sixth week, is apparently similar to that of seventh-week or eighth-week origin previously described for mongolism. This similarity suggests that these particular defects in the embryo may be caused by any of a number of possible mishaps, in themselves unrelated but exerting the same kind of effect on the

differentiating tissues. The anatomic structures involved are those that take shape at approximately the above-mentioned embryonic age.

The agents to be tested as causes of the anomalies are grouped in three categories. These are infectious agents such as rubella and syphilis, chemical agents such as nutritional deficiencies and toxic and metabolic disturbances, and such physical agents as mechanical trauma and structural disease of the uterus. In no case did the tracheoesophageal defect appear in successive generations or recur in the same generation of a family. Suggesting the diversity of the defects resulting from rubella were the associations also observed with anomalies of the cardiovascular, gastrointestinal, genitourinary, respiratory and skeletal systems.

The observation that illegitimacy was associated in an unusually large percentage of the cases studied suggests the possibility of an occasional connection with attempted abortion by mechanical or chemical agents. Instead of the abortion being accomplished, the fetus was possibly rendered defective.

The hypothesis that has been developed is that certain commonly grouped defects representing deviations from normal development during the second month of embryonic life are caused by agents acting through the mother and placenta. This hypothesis must be further tested, for "the question at issue not only is one of specific etiology but also involves principles underlying the larger phenomenon of acquired congenital malformations." Such testing can only be done effectively by a team, the members of which possess collectively more skills and training than any one man can usually master in a lifetime. The authors have availed themselves of the lifetime experience of Dr. Frederick T. Lewis in the field of embryology. The 18 1-mm embryo featured was considered as "probably normal" for thirty-eight to forty days in C. S. Minot's *Textbook on Embryology*, published in 1910. Its sections, one of which is reproduced for the first time in this issue of the *Journal*, provided perhaps the first recorded case of tracheoesophageal fistula in a small embryo.

EMETINE IN ALCOHOLISM

THE publication, elsewhere in this issue of the *Journal*, of a fatal case following the use of emetine hydrochloride in the conditioned reflex treatment of chronic alcoholism sounds a timely warning. Emetine is a drug that may on occasion be toxic to the myocardium, presumably in proportion to the patient's sensitivity to it, and certainly in proportion to the dose administered.

Toxic manifestations of the severity reported by Dr Kattwinkel are fortunately rare. Patients should, nevertheless, be subjected to the most rigid regime when on this treatment.

Dangerous reactions to the drug may be avoided, as suggested by the author and other authorities, by careful preliminary examination of the patient, including an electrocardiogram, in order to eliminate obviously poor risks, by his absolute rest in bed during the course of treatment and for the following four weeks, by careful observation for the signs or symptoms of diarrhea, fatigue, dyspnea on exertion, muscular tremors or weakness and dizziness, and by repetition of the electrocardiogram after the fifth grain of emetine has been administered, at the completion of the course of treatment, and two or three weeks later.

These precautions make the treatment reasonably safe as demonstrated by the large series of patients treated at the Washington Hospital in Boston and at the Shadel Sanitarium in Seattle, Washington. Observations at the Washington Hospital indicate that even in the rare cases in which cardiovascular and other manifestations have occurred, adequate measures, when instituted early enough, have led to complete recovery of the patient from the toxic reaction.

THE SHORTAGE OF NURSES

THE April and June, 1949, issues of the *Harvard Medical Alumni Bulletin* contain a remarkable essay entitled "The Shortage of Nurses." It is that part of the reminiscences of Harvard's oldest alumnus which is pertinent to this aspect of medical care. This is no new issue, but one with which the medical profession and the community have contended, with varying success and much failure, over a long

period. Here an eminent physician whose experience spans an eighty-year period, and whose memory in his nineties is remarkably lucid, tells of his effort and that of others to establish what the doctors of this century have come to accept as a standard institution — the training school for nurses.

One may not conclude that Dr Worcester altogether approved of developments as they took place. It is well known that the emphasis placed upon hospital schools for hospital purposes met with his vigorous warning, and he has long believed that with few exceptions the needs of the community were being neglected. Although it is true that the hospital has tended to neglect the needs of sickness in the home, it has on the other hand taken upon itself the responsibility of caring for many disorders formerly confined to home care.

In many communities this tendency has created a new paragraph in the minimum standard of living. Particularly in the urban areas, the people have come to consider that hospital care is an essential and inevitable service, to a much greater extent than it used to be and, perhaps, than it actually needs to be. The coming of the Blue Cross and the propaganda for "free medical service" is bringing to the minds of vast numbers of people a realization that hospitals are expensive places in which to live. The training of nurses in hospitals was once considered an economic stratagem, but it is no longer so. The training of nurses has become so expensive that many hospital schools are now silently folding their tents.

Dr Worcester's reminiscences have a peculiar historical and practical significance at this time. They indicate a primary responsibility on the part of the medical profession that his generation recognized and carried. Is nursing still fundamental to the care of the sick? It is true that times have changed, and there are different problems to contend with, but somewhere the same zeal, the same burning desire to find a better way, if not a solution, to the present shortage is needed. For fifty years the medical profession has moved in the direction of raising educational standards for the training of nurses, at the same time resisting most serious attempts to produce another, less highly trained,

attendant type of nurse. Should it not consider moving now in the other direction?

The *Journal* salutes Alfred Worcester for his long life of usefulness to others, for the enthusiasm with which he has met the challenges of the profession and for the clarity with which he has retained his interest in its problems.

CORRESPONDENCE

STATEMENT FROM MR. BARUCH

To the Editor: The statement has frequently been made that Mr. Bernard M. Baruch is in favor of compulsory health insurance. In view of this, will you be kind enough to publish the accompanying letter?

Dr. Madge C. L. McGuinness,
51 East 87th Street,
New York, N. Y.

My dear Dr. McGuinness:

What I don't understand in all this talk about medicine is that everybody wants to go to the Government, even our own friends, to get aid. Yet they expect that the Government is not going to call the tune as long as it pays the piper. I certainly do not want to see what is generally known as socialized medicine. As I said at the time of my address, I would oppose it with all my might. I said, as you may remember, that the doctors have to get a move on themselves to meet the needs of the situation, and I stand on my speech. I know that men like Dr. Rawls are doing all they can to meet the needs of the situation without destroying the benefit the world derives from the great service the medical profession has always rendered.

Yours very truly,
(Signed) BERNARD M. BARUCH

MADGE C. L. MCGUINNESS, M.D.
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To the Editor: Some months ago I received a letter from Dr. Channing Frothingham criticizing my inaugural address and threatening to go to the medical and lay press if I did not make retractions. This letter I did not believe it worth while to answer.

Dr. Frothingham states that compulsory health insurance will take care of the medically indigent. Mr. F. Donald Kingsley, acting Federal Security Administrator, according to the *New York Times*, made the following statement: "Those unable to work or dependent on public assistance could have their insurance premiums paid by various public or private agencies. Later we hope to find the means of achieving a complete one hundred per cent coverage of the population." Dr. Frothingham and his cohorts should get together.

Perhaps Dr. Frothingham considers the statements of his co-workers more authentic than the findings of the Brookings Institution. I don't. Regarding compulsory health insurance or socialized medicine, or both, Dr. Ernest E. Irons, former president of the American College of Physicians and president-elect of the American Medical Association has said:

To assert that the proposed program, as implemented in the Wagner-Murray-Dingell Bill, is not socialized medicine is no compliment to American intelligence. We are confronted with an attempt to impose socialized medicine on a people who do not want it. It is a fight that is much more than the fight for the freedom of American medicine. It is a fight for the preservation of American democracy and the American way of life.

Dr. Frothingham criticizes me for not finishing a quotation I made from Mr. Baruch's speech. The amusing part is that the Committee for the Nation's Health (Dr. Frothingham, chairman) has unimished quotes on its pamphlet with Mr. Baruch's picture. For example: "The public is demanding better and more medical service through some action—political or otherwise." (Addendum: "We must look for what can be done and do it. The great question is how. I do not want to seem to say, I know the answers.") "It can be devised, adequately safeguarded, without involving what has been termed 'socialized medicine.'" (Addendum: "The means can be met as in other fields, without the government taking over medicine—something I would fiercely oppose.") Dr. Frothingham states that Mr. Baruch proposed compulsory health insurance. That is not true. He did not advocate a compulsory health insurance scheme as envisaged by Dr. Frothingham or the Wagner-Murray-Dingell Bill. Mr. Baruch stated: "For those who cannot afford voluntary insurance, some form of insurance partly financed by the government covering people in by-law, I would call this compulsory health insurance, if that term's proper meaning had not been lost." What troubles me most are the needs of that sizable segment of society which does not earn enough to pay for voluntary insurance.

Dr. Frothingham gives a list of what he terms prominent people who are in favor of compulsory health insurance. Two of these were listed as sponsors of the recent cultural peace conference held in New York. Three doctors listed as sponsors of the conference are also listed as directors of the Committee for the Nation's Health. The papers during the conference were sufficiently explanatory, and nothing I might add would be more informative than the statements of the State Department, the press and the placards of the pickets.

In view of the happenings of recent months, does anyone question that employees of the Social Security Board are agitating for compulsory health insurance? Are employees of the Government paid to agitate or lobby for anything that is not a law of this country?

Concerning the Tokyo Mission, Mr. Harness quoted a letter from Mr. Wandel, which said in part, "We now think that our need is for someone who is primarily not so much an economic analyst as one versed in health insurance. Health insurance is the major field of social security in Japan; permanent revision requires amalgamating National Health Insurance with Health Insurance on a compulsory basis." Do we need more?

The Committee for the Nation's Health is a lobby and employs paid lobbyists. My purpose was to publicize this fact. I have accomplished my purpose.

I could refute all Dr. Frothingham's statements, but they are so utterly without foundation that to do so would be a waste of my time and of valuable space in your journal. Suffice it to say that my inaugural address has served to awaken the medical profession in New York. Dr. Frothingham and his cohorts are disturbed over my address because it gives facts that they cannot refute. We know and understand their tactics and are not afraid to meet them anywhere, any time, any place. We have them on the run, and all their unfounded claims are comparable to an animal in its death throes that lashes out in all directions. But let me warn those who would destroy the freedom of medicine and eventually all freedom in this country that we haven't yet begun to fight.

WILLIAM BRYANT RAWLS, M.D.

Medical Society of the County of New York
2 East 103rd Street
New York 29, New York

NOTICES

ANNOUNCEMENTS

Dr. Franklin P. Lowry announces the removal of his office from 313 Washington Street, Newton, to 62 Walnut Park, Newton, on July 1.

Dr. James G. Simmons announces that Dr. Fred W. Benton is now associated with him in the general practice of medicine at 30 Myrtle Avenue, Fitchburg.

(Notices concluded on page xv)

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MIGRATING THROMBOPHLEBITIS ASSOCIATED WITH CARCINOMA*

EDWARD A. EDWARDS, M.D.†

BOSTON

AN apparently idiopathic thrombophlebitis may be associated with visceral carcinoma. In most cases the thrombosis is secondary to direct invasion by the tumor. There are other apparently rare cases in which multiple segments of vein are attacked at a distance from the tumor or its metastases. In these circumstances, the venous disorder takes on a particular form, unique for the great number of veins involved, the tendency for migration of the process from one segment to another, its persistence and its tendency to recrudescence. The affected veins show no invasion by tumor, and little reaction of any type. Some change in the blood favoring thrombosis has been assumed, but not demonstrated. The term "migrating thrombophlebitis associated with carcinoma" is suggested to designate the syndrome. Six cases personally observed are described below. One of these has been previously reported.¹

The first description of the disease is attributed to the most writers to Trousseau.² It is probable that Trousseau was emphasizing the association of carcinoma with other and more usual varieties of thrombophlebitis. This matter has been discussed in a previous paper,¹ but may be mentioned again to place the condition in sharper focus. The presence of carcinoma materially increases the incidence of ordinary postoperative and postinfectious thrombophlebitis. Secondly, a vein surrounded or infiltrated by tumor usually undergoes thrombosis. Such a process is commonly observed in the iliac or subclavian veins, when the pelvis or thoracic inlet is the site of metastatic carcinoma. Thirdly, "migrating thrombosis" may occur in the large veins and even in the cardiac chambers, as an expression of terminal debility in patients dying of neoplasm.

The earliest clear description of the form under discussion was presented in 1900 by Osler and McCrae,³ who cited a previous report by Gouget.⁴ Further reports did not appear for many years.^{1, 5, 14}

In 1938 Sproul,¹⁵ by an analysis of 4258 autopsies on patients with cancers of varied origin, found that multiple venous thrombosis was present in 31 per cent of the cases of carcinoma of the body or tail of the pancreas, 10 per cent when the lesion was in the head of the pancreas, 25 per cent when it was in the lung, and 13 per cent when it was in the stomach. In Sproul's series, no other variety of tumor was associated with thrombosis in more than one vein. Kenney¹¹ has recently reviewed a smaller series of autopsied cases and reached similar conclusions.

The reports of 23 cases,^{1, 11-14} which may be classified as migrating phlebitis associated with carcinoma observed during life, in addition to the 6 cases here reported, have been reviewed. In the total of 29 cases, the primary site of the cancer was in the tail or body of the pancreas in 16, the stomach in 4, the lung in 4, the gall bladder in 2 and undetermined sites in 3.

CASE REPORTS

CASE 1.† C. W., a 54-year-old farmer, suffered from pain in the epigastrium and chest, gaseous distress after meals, nausea, weakness and weight loss. Four months after the start of the symptoms, multiple, migrating phlebitis, lasting 5 weeks at each site, developed. In 3 months, he had three attacks in each leg, two in each arm and one in the left external jugular vein.

Physical examination disclosed emaciation, acute and subsiding thrombophlebitis in several areas and an enlarged lymph node in the left posterior cervical triangle. Anemia was present. X-ray study revealed calculi in the left kidney and ureter, with some hydronephrosis. The urine diastase was greatly increased (495 units).

Biopsy of the cervical lymph node showed a well differentiated mucus-secreting adenocarcinoma, interpreted as metastatic from a carcinoma of the body or tail of the pancreas.

A thrombophlebitis occurred in the right iliac vein. The patient gradually grew weaker and developed jaundice. He died suddenly, 10 months after the onset of symptoms attributable to the tumor and 6 months after the beginning of the phlebitis. No autopsy was performed.

CASE 2.‡ B. A., a 49-year-old physician, complained of severe pain in the interscapular region. Three months later, he began to suffer severe abdominal cramps and diarrhea. He abandoned his practice and drifted into semi-invalidism. Thrombophlebitis, which first occurred 7 1/2 months after the onset of the illness, involved the superficial and deep veins of one

*Previously reported.¹

†In the latter part of his course this patient was under the care of Dr. Regina H. Smithwick, who kindly made his records available.

*From the Department of Surgery, Tufts College Medical School. Aided by a grant from the Chariton Research Fund, Tufts College Medical School.

†Instructor in surgery, Tufts College Medical School; clinical assistant in anatomy, Harvard Medical School; consultant in peripheral vascular diseases, Joseph H. Pratt Diagnostic Hospital and hospital of the Massachusetts Soldiers' Home; surgeon-in-charge, Vascular Clinic, Boston Dispensary.

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Dr Frothingham gives a list of what he terms prominent people who are in favor of compulsory health insurance Two of these were listed as sponsors of the recent cultural peace conference held in New York Three doctors listed as sponsors of the conference are also listed as directors of the Committee for the Nation's Health The papers during the conference were sufficiently explanatory, and nothing I might add would be more informative than the statements of the State Department, the press and the placards of the pickets

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Concerning the Tokyo Mission, Mr Harness quoted a letter from Mr Wandel, which said in part, "We now think that our need is for someone who is primarily not so much an economic analyst as one versed in health insurance Health insurance is the major field of social security in Japan permanent revision requires amalgamating National Health Insurance with Health Insurance on a compulsory basis" Do we need more?

The Committee for the Nation's Health is a lobby and employs paid lobbyists My purpose was to publicize this fact I have accomplished my purpose

I could refute all Dr Frothingham's statements, but they are so utterly without foundation that to do so would be a waste of my time and of valuable space in your journal Suffice it to say that my inaugural address has served to awaken the medical profession in New York Dr Frothingham and his cohorts are disturbed over my address because it gives facts that they cannot refute We know and understand their tactics and are not afraid to meet them anywhere, any time, any place We have them on the run, and all their unfounded claims are comparable to an animal in its death throes that lashes out in all directions But let me warn those who would destroy the freedom of medicine and eventually all freedom in this country that we haven't yet begun to fight

WILLIAM BRYANT RAWLS, M D
Medical Society of the County of New York
2 East 103rd Street
New York 29, New York

NOTICES

ANNOUNCEMENTS

Dr Franklin P Lowry announces the removal of his office from 313 Washington Street, Newton, to 62 Walnut Park, Newton, on July 1

Dr James G Simmons announces that Dr Fred W Benton is now associated with him in the general practice of medicine at 30 Myrtle Avenue, Fitchburg

(Notices concluded on page xv)

From this time to death 7 months after the onset of the thrombophlebitis, the inflammation smoldered in the previously involved veins.

Autopsy, performed by Dr Michael MacKenzie, revealed that the adenocarcinoma had invaded the portal vein and extended into the branches of this vessel in the liver. The liver lymphatics were likewise invaded. The pancreas was not involved. There were multiple infarcts of the kidney and spleen dependent upon thrombosis of fine veins. The iliac veins and the vena cava to the level of the ligature showed an organizing thrombus. Nowhere except in the portal vein was there invasion of the veins by carcinoma. Inflammation was found only in limited zones in the walls of the veins. Here and there a few eosinophils were evident.

DISCUSSION

Clinical Features

Patients with this syndrome are of middle or old age, and of both sexes, men predominating. The patient may present himself because of the venous disease while the carcinoma is unsuspected.

Inflammation of the superficial veins of the legs or forearms is the usual initial complaint, even though one may deduce from the pathological material that many deep veins may be involved early. Thrombophlebitis is apt to be present in the saphenous system at the ankles, extending somewhat onto the dorsa of the feet, a territory ordinarily affected only in the migrating phlebitis of thromboangitis obliterans. I have not seen the process extend to the distal portion of the foot or onto the toes, however, as it does in thromboangitis obliterans. Deep calf tenderness and edema suggest involvement of the deep veins of the leg, and pain over the sacral or hip regions suggests pelvic phlebitis.

The thrombophlebitis appears at one or more sites at the outset. The process then extends here and there, often for distances such as from the ankle to the groin, whereas the initial segment may become quiescent, or may show a continuous inflammation for days or weeks. A quiescent area is prone to become inflamed again at almost any time in the disease, and pathological examination indicates that this represents recurrent thrombosis. As in other forms of thrombophlebitis, there is great variation in both local and general signs of reaction. Temperatures up to 100.5°F are common, though the white-cell count is generally unchanged. In my experience, the fever is uninfluenced by penicillin, as in the usual nonseptic forms of thrombophlebitis.

Multiple pulmonary emboli are very common, though often small and unrecognized. In 1 case (Case 5), the disease was probably first announced by a small pulmonary embolus. This tendency to emboli should be kept in mind particularly in the postoperative state.

As time goes on, the thrombosis becomes more extensive, with involvement often of much of the portal system, of the inferior vena cava and many of its tributaries, and still more of the veins of the extremities. The thrombosis may thus hasten the death of the patient, through pulmonary embolism

and through serious injury of viscera, which are more sensitive to venous occlusion than the peripheral parts. The thrombosis in the peripheral veins was extensive enough, however, to cause gangrene of the foot and toes in 1 case (Case 3).

The lack of arterial thrombosis is noteworthy.

Is the patient always doomed once the thrombophlebitis is detected? The thrombophlebitis has already been defined as one in which carcinoma evidently does not invade the involved segments of veins. This may be concluded from the examinations, by biopsy or at autopsy, in the cases reported. Moreover, evidences of blood-borne metastases, outside the probable portal-vein dissemination, have not been disclosed in the affected patients. Therefore, so far as the venous lesion is concerned, it should be possible for the patient to recover if the carcinoma were removable. Yet the carcinoma proved to be inoperable, by the time its presence was recognized, in every case reported, and the patient died within some weeks or months of the onset of the thrombosis. This was true whether the patient's first symptoms were related to the venous process or to the visceral lesion. It remains to be seen whether future earlier recognition of the syndrome, with immediate surgical intervention, will mitigate or reverse the present unfavorable prognosis.

Thrombogenesis

The cause of the thrombosis is unknown. It has already been emphasized that there is no malignant infiltration of the vessel wall. Inflammation of the wall is likewise generally absent, though in some areas one may find foci of a few polymorphonuclear leukocytes, lymphocytes, plasma cells and fibroblasts. This corresponds to the picture seen in the ordinary bland thrombophlebitis of the recumbency state. Sproul¹⁶ suggests that a few cancer cells, which metastasize to the vein and initiate the thrombosis through their local secretory activity, may be overlooked. This appears unlikely in the face of the rarity of metastatic growths in the periphery. Slowing of the blood stream, generally considered important in thrombogenesis, is likewise lacking, except in the splenic vessels actually surrounded by tumor.

This leaves the possibility that the determining factor is some unusual change in the blood, owing possibly to a material generated by the tumor. So far, no changes in blood coagulation have been revealed in the cases reported, though the studies have admittedly been far from exhaustive. It has been pointed out that a characteristic common to the cells of the tumors responsible is that they are mucin secreting. The existence of mucin has not been determined in all the tumors reported, and yet it would not be unusual to find some mucin formation by tumors all entodermic in origin. Still,

leg. Within four weeks, the process advanced to new areas in the same leg and spread to the other leg and to both upper extremities.

Significant clinical findings consisted of an increased serum bilirubin, evidence of impaired liver function and the presence of occult blood in the stool. The urine diastase was normal until just before death. Exploratory laparotomy was refused.

The patient's course was characterized by another attack of thrombophlebitis in the superficial veins of one arm, a deepening jaundice and, finally, ascites. He died 13 months after the onset of symptoms of the tumor, and 5 1/2 months after the first attack of thrombophlebitis.

Autopsy, performed by Dr. Rudolph Osgood, showed an adenocarcinoma of the pancreas, with extension about the hilus of the liver, and metastases to that organ and to the celiac lymph nodes. There was thrombosis of the portal vein, and the right femoral and both common and external iliac veins. No carcinoma was demonstrable in the veins, except in those traversing the tumor.

CASE 3 A D, a 57-year-old photoengraver, complained of upper abdominal distress, bloating after meals and loss of appetite. Three months later, he began to experience severe abdominal pain occurring in bouts, especially at night. Constipation became marked. He lost 5 pounds in weight. Thrombophlebitis first appeared in the superficial veins of both forearms and in the left leg 6 months after the onset of the abdominal symptoms. Five weeks later, and while the initial thrombophlebitis was still active, he suffered an erysipelas-like attack in the right leg, seemingly as an allergic reaction to epidermophytosis of the foot. A second attack of phlebitis in the veins of this leg was noted in a few days. This was quickly followed by a third attack in the superficial veins of the left forearm. Biopsy of the latter lesion showed a bland thrombosis.

Significant findings relating to the tumor consisted of a palpable liver edge and evidence of impaired liver function. Neither diastase nor lipase was increased in the blood or urine. A diagnosis of carcinoma of the tail of the pancreas was made. Laparotomy was performed 8 months after the onset of tumor symptoms, and 2 months after the initial attack of thrombophlebitis. An inoperable adenocarcinoma of the tail of the pancreas was found, with metastases in the liver and peritoneum.

Postoperatively, the patient showed increasing emaciation, jaundice and swelling of the abdomen. There was evidence of thrombosis of the deep veins of the lower limbs to the iliac level. One week prior to death, he developed gangrene of the left foot. He died 9 months after the first appearance of abdominal symptoms, and 3 months after the initial attack of thrombophlebitis.

Autopsy, performed by Dr. Philip Le Compte, showed extension of the carcinoma from the tail of the pancreas to the celiac lymph nodes and nerve plexus. The metastases to the liver had broken through to the right perinephric tissues and diaphragm. There was invasion with thrombosis of the splenic artery and vein as they traversed the tumor.

Recent and old thrombosis, without tumor invasion, was widespread in both the portal and the inferior-vena-cava system. The lungs showed a number of old and recent emboli of the smaller arteries with multiple infarcts. Thrombosis was present in the tributaries of the splenic vein, with splenic infarcts. A fresh thrombosis was also present in the upper superior mesenteric, midcolic and upper jejunal veins. The upper 40 cm. of the jejunum was gangrenous. The middle of the gastroduodenal venous arcade and its tributaries showed fresh thrombosis. The process involved the inferior vena cava from just below the renal veins continuously down both common and the left internal iliac veins, both external iliac and femoral veins and the superficial and deep veins of the lower limbs. Though the main renal veins were spared, the smaller veins of both kidneys were extensively involved, with resultant infarcts. There was extensive thrombosis of the prostatic veins, with evidence of superposition of at least three attacks. The process in the legs was examined in detail. No arterial occlusion was found, and the gangrene of the left foot was therefore attributed to the extensive and repeated venous thrombosis in the limb.

Only where the splenic vessels traversed the tumor was there evidence that cancerous infiltration was responsible for the thrombosis. Otherwise, the thrombosed veins generally

showed an absence of reaction, with scattered zones of infiltration with polymorphonuclear leukocytes or lymphocytes. The recurrent nature of the thrombosis was indicated by the variation in the age of the process in different segments of the veins and, in some areas, by thrombosis in vessels recanalized from a previous episode. The tendency to thrombosis did not extend to the arteries. The involvement of the splenic artery was hardly an exception, since such a process within a tumor is commonplace.

CASE 4 E P, a 52-year-old machinist, complained of pain in the lower thoracic portion of the back with a feeling of pressure across the chest. His appetite had become poor and he lost 30 pounds of weight in 3 months. Two and a half months after the onset of his illness, a thrombophlebitis appeared in the deep and superficial veins of the right foot. Two weeks later, the process extended to the vessels of the upper right calf.

X-ray examination showed a lateral and anterior displacement of the cardia of the stomach. The blood and urine amylase and lipase were not increased. A diagnosis of carcinoma of the tail of the pancreas was made. At laparotomy, an inoperable adenocarcinoma was found in this location, with metastases in the liver.

At the time of this report, the patient is alive, 4 months after the onset of symptoms attributable to the tumor and 1 1/2 months after the onset of the thrombophlebitis.

CASE 5 W G, a 56-year-old machinist, suffered an attack of phlebitis in the left leg, lasting 1 week and associated with a small pulmonary embolism and infarction. Ten days after the initial attack quieted down, a similar process developed in the right calf, lasting 3 weeks. A month later, a third attack developed at the right ankle, migrating through the superficial and deep veins of the right leg. The patient was working and in good condition when seen. He denied any symptoms except those referable to the thrombophlebitis. Hospital study revealed only an anemia. Another attack of phlebitis, involving the superficial veins of the right calf and the left thigh, developed during the period of observation.

Exploratory laparotomy was performed 3 months after the onset of the thrombophlebitis. An inoperable carcinoma of the stomach was found, with metastases to the liver. The pancreas was not involved. Thrombophlebitis was evident postoperatively in the superficial veins of the right upper limb and later in the deep veins of the left leg and foot. In the last months of life, there was recurring inflammation in many veins previously involved.

The patient died 6 months after the first attack of thrombophlebitis. No autopsy was performed.

CASE 6* C C, a 38-year-old machinist, had suffered a thrombophlebitis in the superficial and deep veins of the left leg. He had been given penicillin in oil intramuscularly. After the third dose, a generalized, itching rash developed, and the medication was discontinued. The phlebitis quieted down after rest, but recurred on return to work. Two months after the onset of the illness, the veins of the right leg were involved. A month and a half later, he suffered a small infarction of each lung. The superficial and deep veins of the left upper limb and then the superficial veins of the right forearm became thrombosed. This was followed by a phlebitis of a vein in the left flank.

Biopsy of a vein from the left forearm showed an angitis with an exudate rich in eosinophils. The white-cell count was 10,400, with 12 per cent eosinophils. Periarteritis nodosa was suspected, the penicillin in oil being the possible etiologic agent. Examination revealed no findings to suggest visceral carcinoma. A single, large gallstone was seen on x-ray study.

A month later, thrombophlebitis developed in a supra pubic vein and then in a vein in the right thigh. At this time, jaundice was noted. The eosinophil count had fallen to 8 per cent. A third and larger pulmonary infarction occurred, and the inferior vena cava was ligated.

Ten days later, there were signs of a cholecystitis and a laparotomy was done, 4 months after the first attack of thrombophlebitis. An inoperable carcinoma of the gall bladder was encountered extending into the lesser omentum and to the hilus of the liver, with direct extension and metastases in that organ.

*Reported through the courtesy of Dr. Walter Garrey.

thrombosis in a patient with carcinoma, the thrombosis of a vein involved in the tumor or its metastases or a marantic thrombosis in a patient dying of neoplasm.) The involved segments in the process show neither neoplastic infiltration nor any other characteristic finding. The veins of both the upper and lower extremities are involved early, and the intra-abdominal veins at some time of the disease. The latter may lead to visceral necrosis. Once the process has started, new attacks, and recrudescence in previously involved segments, occur rapidly until the death of the patient. The great extent and recurrent nature of the thrombosis were indicated in 1 case by the production of gangrene of the foot seemingly through the venous process alone. Pulmonary embolism is a common complication.

The initial lesion is most often a carcinoma of the pancreas — especially of the tail or body — or less often, carcinoma of some other viscus.

The thrombophlebitis must be differentiated from the migrating phlebitis of thromboangitis obliterans, and the more common "idiopathic thrombophlebitis," in which no associated causal factor can be discovered. The presence of an idiopathic thrombophlebitis with the apparent characteristics of the variety associated with carcinoma is an indication for intensive investigation to discover the neoplasm, including an exploratory laparotomy in some cases. The question of whether or not the carcinoma is ever removable when the thrombophlebitis has already appeared is so far unanswered.

I have recently seen a seventh case through the courtesy of Dr. F. S. Homburger. The patient was a seventy-two-year-old man. The carcinoma was located in the head of the pancreas, with migrating phlebitis of both legs, beginning six months after exploration had revealed an inoperable tumor.

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A MEDICAL SURVEY OF THE ALEUTIAN ISLANDS (1948)*

FRED ALEXANDER, M.D.†

BOSTON

THE early health beliefs of the inhabitants of the Aleutian Islands, a territory of the United States stretching in a broken chain from the western end of the Alaskan Peninsula to Kamchatka off the eastern coast of Siberia for a distance of about 1200 miles, are described by Veniaminov as follows:

The old men taught that whoever should talk badly about the sun, that for instance it heats too much, or hides itself too much, etc., will be blinded by it and not allowed to see its light. The moon will slay its detractor with a stone. And he who talks badly about the stars will be forced by these to count them, failing in which he will lose his mind.

From many beliefs relating to health, long activity, etc., I know only that the fathers and uncles endeavored to get the saliva of some old man, most famous by his undertakings and faultless life, as well as healthy and brave, and such saliva they gave to their children to swallow as a preventive from infections and epidemic diseases and as a means for strengthening the bodily powers. Such old men at their death regaled their grandsons by some of their hair or a part of their garments or

the weapon which they carried in their encounters and commanded them to carry these on all occasions so as to prevent misfortune in every thing as well as health.

Many of these one hundred larger and smaller islands are clearly remembered by those in the armed forces stationed in this mountainous, rough and inhospitable terrain, not only because of the almost continuous drizzle and fog, the temperature rarely below 0°F or above 70°F in the shade, and the winds of intensities well over 100 miles per hour but also for the beauty of an unharnessed nature. Many of the islands are piled up around volcanic masses ranging from an unapproachable structure of gray-white, hard granite to a huge mountain peaked by a snow-capped cone resplendent in its halo of clouds and rare sunshine.

Very little is known of the habits of these island people before the influx of Russian culture around 1741. Veniaminov, a Russian priest of great ability and esteem, spent ten years with the Aleuts (1824-1834) at a time when there had already been an eighty-year contact with the white men, so that

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†Clinical and research fellow, Massachusetts General Hospital.

this merely emphasizes a category of tumors and does not explain the thrombosis

The production of digestive enzymes in the presence of tumors of the pancreas has received special attention. This subject is carefully reviewed by Sproul¹⁵. The tumors of the tail or body are apt to be associated with an overabundance of enzymes in the circulating blood, whereas those of the head, by obstructing the ducts, may cause a diminution in output. It is considered possible that an increased production of enzymes hastens blood coagulation, directly, or indirectly — by facilitating absorption of materials used in the process. Sproul suggests that in cancer of the stomach an achylia gastrica would provide a more favorable medium for the action of the normal pancreatic enzymes. It is my belief that an increased quantity of enzymes in the blood stream might damage the endothelium. This has not been brought out by the determination of lipase and amylase in the early stages of the cases described, but the proteases might be more significant. Unfortunately, no good tests are at present available for the measurement of these enzymes.

Diagnosis

The diagnosis of migrating thrombophlebitis associated with carcinoma is a problem first of ruling out known causes for thrombophlebitis, and then of differentiating various types of idiopathic thrombophlebitis. At the outset, one should carefully exclude usual and adequate causes of the venous disorder. Particular attention should be paid to the presence of varices, a point often difficult to decide when the varices are small. The history may suggest direct invasion of the iliac or subclavian veins by tumor, particularly if a gradually developing lymphatic edema has preceded evidence of venous thrombosis. A thorough physical examination may demonstrate a mass in the thorax or pelvis responsible for such a process. Laboratory studies will help in disclosing a neoplasm or blood dyscrasia.

In most patients in whom a usual cause is not readily found, no specific disease connection will ever be disclosed, and the diagnosis will finally be true "idiopathic thrombophlebitis," so called. But before this diagnosis can be established with reasonable certainty, thromboangitis obliterans and visceral carcinoma must be ruled out.

The *thrombophlebitis of thromboangitis obliterans* closely resembles that associated with carcinoma. The criteria for the diagnosis of the former variety have been emphasized in another paper¹⁶. The patient is generally a much younger person (in the twenties or thirties) who almost invariably uses tobacco. The phlebitis, which is migrating and recurrent, is evident in the same veins as those in the cases associated with carcinoma, *its progress from one area, or one vein to another, is not as rapid or as extensive*. The arteries may or may not have been involved at the time the patient is seen. Biopsy

of an inflamed vein often shows a characteristic intraluminal granuloma.

Patients with the thrombophlebitis associated with carcinoma are ordinarily in their late forties, or older. The diagnosis may be indicated by the multiple migrating and recurrent nature of the process, and is established by the finding of a visceral carcinoma that has not demonstrably invaded the involved veins. The disorder may be suspected when but a single vein is thrombosed, but it is highly improbable if the process does not spread to other segments within a few weeks of the first attack. Furthermore, if months or years have elapsed between a previous attack and the present one, the case is probably one of truly idiopathic thrombophlebitis. Biopsy has so far given no characteristic picture, but may be helpful in ruling out thromboangitis obliterans.

Treatment

Treatment is of secondary importance to the search for the responsible neoplasm. It is evident that suspicion rests on several organs, especially the pancreas, stomach and lung. Diagnostic procedures should be vigorously prosecuted. It is my conviction that exploratory laparotomy should be performed if the presence of a carcinoma is not established otherwise.

SUMMARY

Six personally observed cases of a multiple, migrating and recurrent thrombophlebitis associated with visceral carcinoma are reported. Four of the patients showed carcinoma of the tail or body of the pancreas, 1 a carcinoma of the stomach, and 1 a carcinoma of the gall bladder. In 2 cases the thrombophlebitis was the initial complaint, in the others, it started two and a half to seven and a half months after the onset of the illness.

The thrombophlebitis was a late sign of the carcinoma. Laparotomy was performed in 4 cases and revealed an inoperable carcinoma, three and four months, respectively, after the onset of the thrombophlebitis, in the patients in whom that was the initial complaint, and one and a half and two months after the first attack of phlebitis, in the patients in whom the initial symptoms were referable to the tumor itself. One patient is now alive one and a half months after the onset of the thrombophlebitis — the others died three to seven months after their first attack.

Two patients showed disorders that were probably allergic in nature — 1 an erysipelas-like reaction with a fungous infection of the foot as the possible initiating agent, and the other a condition resembling periarteritis nodosa, with administered penicillin in oil as the likely causative factor.

The term "migrating thrombophlebitis associated with carcinoma" is suggested for the syndrome. (The term is not meant to include a recumbency

thrombosis in a patient with carcinoma, the thrombosis of a vein involved in the tumor or its metastases or a marantic thrombosis in a patient dying of neoplasm.) The involved segments in the process show neither neoplastic infiltration nor any other characteristic finding. The veins of both the upper and lower extremities are involved early, and the intra-abdominal veins at some time of the disease. The latter may lead to visceral necrosis. Once the process has started, new attacks, and recrudescence in previously involved segments, occur rapidly until the death of the patient. The great extent and recurrent nature of the thrombosis were indicated in 1 case by the production of gangrene of the foot seemingly through the venous process alone. Pulmonary embolism is a common complication.

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†Clinician and research fellow, Massachusetts General Hospital.

perhaps none of his Aleut informers could speak directly of the pre-Russian experiences and culture. Data concerning the appearance of various diseases among the islands with the coming of the Russians have been compiled by Veniaminov and others, including Blaschke, — the first Russian doctor to be sent to the Aleutians in 1835, — and such information has been quoted in this review.

Syphilis and other venereal disease, smallpox, consumption, measles, scurvy, influenza, pneumonia and possibly typhoid fever all made their appearance with the introduction of the new culture. Each newly arrived ship was a potential source of infection for some strange new disease. Because of his lack of immunity to these invasions, the Aleut served as excellent culture material. Diseases that were easily cared for among the white inhabitants reached immense proportions among the islanders. It was reported that in 1845 an epidemic of measles, assuming the "black form," caused near panic among the inhabitants of Kodiak Island and the contiguous mainland. The health of the villagers was entrusted both to the village priest, or shaman, and to a certain number of select people schooled in the art of healing by principles handed down from generation to generation. Usually, this knowledge was kept in one family group and passed on only to the most deserving.

Smallpox exacted a terrific toll of life in 1838, sweeping across the entire length of the Aleutian chain and actually accounting for the terrible death of half of the Alaskan population. Prior to this time explorers sailing along the coastline were surprised to find pox-marked Aleuts around 1786 and attributed this onset to a visit made by the Spaniards ten years earlier. With such menaces lurking in every direction Petroff was indeed surprised to find the rare Aleut who had reached the age of fifty. Such a discovery in any tribe gave proof to the fact that this person must have been one of rugged constitution in early life. Although freed of the major ills, very few people escaped the annoying complaints of eye disease and possibly rheumatic pains. The former was attributed to the smoke-filled huts, or *barabaras*, which gave rise to almost continuous eye irritation. Many of the women folk used their eyes incessantly for fine needlework and now world-famous basketry in a poor light, and thus visual acuity was greatly diminished early in life. The villagers successfully treated occasional nosebleeds by bending the distal phalanx of the small finger — on the side corresponding to that of the nares emitting blood — on itself and tying it in such a position.

Owing to the rocky terrain, many bare feet of the Aleuts were cut by sharp stones, and it was not unusual to see one man, using a bone needle and sinew, sewing up the wound of another while the patient sat complacently holding his foot in position. To exhibit no outward sign of pain was a mark of merit and strength. Severe cuts and burns were

usually treated with warm fish oil, warm fresh fox grease or some similar substance. Deep wounds were dusted with parched powdered teeth, the hole being covered with a fresh skin of a mouse. Fractured bones called for the use of splints made from animal bones or driftwood.

In the treatment of dangerous wounds or diseases the Aleut employed both patience and diet. Such conditions were supposedly aided by a complete fast — allowing not one drop of water or any food for two to four days in sequence. To one in such a state, it was believed that food and drink led inevitably to inflammation and death. The intimate knowledge of the use of herbs was essential in the treatment of some ills. For swellings and rheumatic pains various poultices and warm, baked roots were used locally. Fevers were "cured" with bitter concoctions, and diarrheas with astringent herbs. Sore throats and stomach aches were also amenable to similar brews. Warm roots were applied to the chest of one who had complained of pain therein. Some of the local village doctors went through the motions of attempting to sew the lung up inside by actually sewing with thread a small area of the chest overlying the pain. A form of cupping was also used, suction being applied by way of mouth.

Lancing came into practice for cure of chest ailments, and only the artful medicine man, whose skill was handed down from generation to generation, was permitted to do this. Stone points were used, and a thorough knowledge of where and how deep to cut was essential. Only critical conditions were treated in this manner. Even colic was said to have been beneficially aided by such a maneuver. At times a slight degree of lancing over any affected area or organ was of noted aid. Blood letting from both hands and feet was a common practice for tiredness, feebleness, loss of appetite and headache. Another form of treatment in common employment was "holding." Practiced by the older women doctors, this consisted of bringing into the proper anatomic order and laying into place all the apparently affected internal organs of a given illness. Such manipulations have not gone without praise even today. The doctor today utilizes his sense of touch to a commendable degree in the diagnosis of various ills. I have seen hypertension suspected because the pulse in a small temporal artery seemed much stronger than normal.

The treatment of kidney trouble is noteworthy. If a person could not urinate he was placed in a vat-like structure of warm water. The water was heated by a small fire under the tub-like apparatus and kept warm by a deposition of sand in the bottom. Another practice, which is still used, is the giving of a glassful of water previously strained through a cloth containing cracked glass. It is thought that this water contains small particles of the glass, which in turn will clean out the small tubes in the kidney itself. Such a belief gave a clue to the fact that the early Aleut had a knowledge of human anatomy.

gleaned, no doubt, from his experience in preparing mummies and his habit of examining the organs of rivals killed during battle. Lutke, in 1827, mentioned this detailed study and knowledge of the anatomy of the human structure. Whether or not the Aleut recognized the difference between an artery and vein before Harvey's time and the circulation of blood is a debatable and interesting point.

Pregnancies were guided to completion by some older woman or female relative. Usually, each village had a midwife schooled in her duties by an older woman. To have her baby resemble a certain person, the pregnant woman had to visualize this person every time she ate or drank. Now and then she underwent the "holding" routine in which everything was put into its proper place. As soon as the child was born the mother was made to assume the squatting position, not being allowed either to lie or to sit down. After the placenta was discharged with the help of abdominal manipulation, the mother's abdomen was tied with a belt or cloth. In turn, she was usually carried to another position and propped up by pads into a squatting position where she remained for four days. On the fifth day she was washed and permitted to lie or sit down but not to stretch her legs. For forty days she was considered unclean and was not allowed to touch anything edible except for her own food, nor could she see any men. If the baby did not resemble the father, family discord, maltreatment and divorce resulted.

At the beginning of menstruation usually at fourteen years of age, every girl was immediately segregated in a special corner of her *barabara* so constructed by the hanging of a curtain or a matting. Small pieces of string were tied around each joint, and she was not allowed out of her corner for any purpose. Usually, she was given plenty of twine or yarn to knit. Visits were made only by her mother or close female friends, and she could show herself to no man. For forty days she remained in the same condition, and was finally allowed to leave to bury her pads but was not permitted to look at the sun. For ten more days she spent her time alone cleaning the house from top to bottom. At this time she was usually taken to the side of a sick boy and thus was able to utilize the curative powers that she thought to manifest at that time. Finally she was freed. If such a tradition went unnoted, it is said that the young lady would eventually turn black as coal and become afflicted with various communicable diseases. Also, unfulfillment of such obligations would drive all living fish and animals away from that particular village, with subsequent starvation of the inhabitants.

EXPEDITION OF 1948

During the summer months of 1948 I had the privilege of accompanying a group of scientists from Harvard University's Peabody Museum into

this unique region. Such an opportunity was afforded me through the generosity and encouragement of Dr Paul D. White. The purpose of the over-all project was an anthropologic and archeologic evaluation of the existent Aleutian culture, and although the medical program dealt primarily with cardiovascular problems, an opportunity to observe the changing customs and trend of disease was afforded the observer.

Evaluation of the dental problems was made by an orthodontist, Dr Coenraad Moorrees, of the Forsyth Dental Infirmary in Boston, and I am indebted to him for any dental information presented.

The population of two villages was studied — people of Nicol'ski on the island of Umank, one of the Fox Island group, and of Atka, a village of the Andreanov Islands. The former included 51 persons, 31 males and 20 females. The average age of the males was twenty-six and one-tenth years, and that of the females twenty-seven and one-tenth, the average age for both sexes was twenty-six and six-tenths years. Of this group, 4 males and 7 females were ten years of age or below, whereas 3 males and 4 females were above fifty years, the average age for both sexes was twenty-five years. The trend of the present rate of reproduction can be seen here. The latter village, Atka, added 66 people to the survey — 33 males and 33 females. The average age was twenty-six and two-tenths years for the males and twenty-four years for the females. Nine males and 8 females were ten years or below, whereas 4 males and 2 females were fifty years or above. All the inhabitants of Nicol'ski were included in 9 family name groups, whereas 11 family names embraced all Atkans. Of these 9 family groups at Nicol'ski all had been visited by tuberculosis, 5 by venereal diseases, 6 by pneumonia, 1 by possible cardiac disorder, 1 by possible cerebral thrombosis, 1 by diphtheria, and 4 by tonsillitis within the past two decades. Tuberculosis claimed as many as 4 victims in 1 family within this period. At Atka of the 11 families 9 were afflicted by tuberculosis, 6 by venereal disease, 6 by pneumonia, 1 by possible renal disease, and 1 by possible heart disease. These diseases of the past were quoted from death records and old church records, together with verbal histories available at the time.

With such a background, physical examinations carried out were most revealing. Steller, a botanist who accompanied Behring on his memorable voyage in 1741-42 described the typical appearance of the average Aleut as follows:

He is of medium stature, strong and square built, with muscular arms and legs. The neck is short and the shoulders broad. The complexion is a ruddy one. Theirs is mostly glossy black hair with only a scant beard or none at all on the chin. In this fact they are similar to the inhabitants of Kamchatka and to other East Siberian natives.

Physical examination revealed the average blood pressure at Nicol'ski to be 128 systolic, 74 diastolic, and that at Atka to be 119 systolic, 72 diastolic. At this point it may be interesting to note some blood pressures taken at typical Eskimo villages (Table 1) and made available to us through the generosity of Miss Heller, a member of the Territorial Department of Alaska. These data are of interest because the anthropologists now believe that the Eskimo is closely related to the Aleut. The average pulse rate among male Aleuts was 66 and that among the females 71. A survey of rampant diseases as evidenced by clinical findings

TABLE 1 Blood-Pressure Values of Eskimo Peoples in 6 Villages and 1 School*

AGE	MALE SUBJECTS			FEMALE SUBJECTS		
	NO	PER- CENTAGE OF ESKIMOS	BLOOD PRESSURE	NO	PER- CENTAGE OF ESKIMOS	BLOOD PRESSURE
yr						
Under 21	50	95	110/69	57	99	116/71
21 to 40	39	86	116/72	63	97	115/72
41 to 60	34	96	102/76	30	93	132/79
Above 60	13	98	126/73	10	100	153/74

*Total of 296 cases

disclosed that tuberculosis, venereal disease, scabies, refractive errors of the eyes, trachoma and dental caries were most prominent. Hypertension (blood pressure above 140 systolic, 90 diastolic, in a moderately young subject fifty years of age or below) was found in only 1 person at Nicol'ski, a forty-three-year-old man with a blood pressure of 204 systolic, 110 diastolic, in the upper extremities and 100 systolic, 72 diastolic, in the lower extremities. He was suspected of having a mild degree of coarctation, and although there was no x-ray apparatus to substantiate this diagnosis, the presence of intercostal pulsations, lack of femoral pulsations, an enlarged heart by percussion, a hypertensive electrocardiographic picture and a lifelong history of trouble with his health led one to suspect that disease. Another man, sixty-six years of age, had a blood pressure of 180 systolic, 100 diastolic, with no clinical signs or symptoms. Table 2 presents the relative percentages of diseases found at both villages. Other conditions included vitiligo, keloid formation, arcus senilis, folliculitis, alopecia, feeble-mindedness, varicosities, kyphoscoliosis, pterygia, a case of possible carcinoma of the stomach, a case of probable beriberi resultant from a long-term period of involuntary encampment in Japan during the war and a case of duodenal ulcer proved by x-ray study in an Army camp. Menstrual disorders were prominent. Cardiac and renal disorders, cirrhosis and multiple avitaminosis were also noted. The degree of dental caries was deplorable. The majority of people had mutilated teeth because of dental decay and subsequent extractions. Mandibular prognathism, with

resultant dental malocclusion, was present to a considerable degree. Gingival and periodontal disturbances and the presence of calculus were found only occasionally. It has been stated by the old native Aleuts that before the advent of sugar and starches the condition of the teeth was excellent and that caries per se was relatively unknown. Such a belief seems to be borne out by the discovery that the teeth found in the skulls of the early Aleuts were without caries as it is now known. Scabies was more pronounced in Atka. This infestation was traced back to the World War II, when the Atkan Aleuts were evacuated to southeastern Alaska. Since that time all attempts to control this problem have been unsuccessful. The general morale seemed to be at a low ebb in this village, possibly because of a shortage of food at the time of the survey and a high incidence of disease and inebriety.

Much more investigative work will have to be done on the dietary program as it exists in this region. At the present time suffice it to say that these people maintain the present degree of nutrition on a diet consisting chiefly of fish and seal meat, sea-lion meat, duck, geese, reindeer meat, blubber and very few vegetables and green foods. They have little if any fruit and very little milk, together with a rather sparse supply of sugar and flour. In a preliminary analysis this diet was relatively high in protein, low in carbohydrate and moderate in fat. Vitamins A, B and D were of a low normal value. Vitamin C was extremely low,

TABLE 2 Diseases among 117 Patients Examined

DISEASE	INCIDENCE AT	
	NICOL'SKI	ATEA
	%	%
Tuberculosis	17.0	22.0
Venereal disease	19.0	17.5
Scabies	0.5	20.0
Hypertension (blood pressure, 140/90)	1.9	0
Cardiac abnormalities	1.9	0
Renal disorders	0	1.0
Cataract	3.9	1.0
Refractive error	23.5	16.0
Cirrhosis	0	3.1
Trachoma	0	6.3

and calcium and iron were both low. The average nutritional value as estimated at present is approximately 800 to 1400 calories per day. Under this regime the average Aleut cannot work hard without a loss of weight and energy, according to American standards. Luckily, at present he does not have to do much to survive in his communal system of living. Before any criteria of comparison are presented, it must be mentioned that results employing American standards would be subject to question because of the short extremities of the Aleuts, both children and adults. With this in mind one can state that the ratio of weight to height in children was high, the absolute weight averaging less than

one standard deviation below what would be expected for comparable normal white American children. The absolute stature, however, was about three standard deviations below average. In adult the ratio of weight to height seemed to fall within normal limits. Further dietary studies will be forthcoming in a subsequent report.

Various chemical studies were carried out on these fish-eating and meat-eating peoples. It was surprising that of 66 nonprotein nitrogen determinations carried out on the Atka people the average result was 59.5 mg per 100 cc; urinalyses were within normal limits. The total proteins in these same people averaged 7.02 gm per 100 cc. Cholesterol determinations were done on 51 Nicolai people and 66 Atkians. The average was 176 mg per 100 cc for the former and 197 mg per cent for the latter. Almost immediately after the blood had been taken the serum was separated by means of a hand-powered centrifuge, stored in the cold, and sent to the Massachusetts General Hospital within a week for analysis. Miss Rourke and her staff at the Chemical Laboratories of the hospital ran a series of controls on cholesterol determination after the samples had been standing one, two, three and four weeks and showed thereby that variations from the original result in this period were negligible, as suspected.

Determinations of basal metabolic rates were attempted but were highly unsatisfactory because of the marked prognathism and the fear of the Aleuts in the use of the apparatus. Furthermore, it was thought that this method would surely be a dangerous procedure in this region of active tuberculosis. Determinations on 17 adults ranged from -10 to +17 per cent, however.

Electrocardiograms were done on the entire group, three limb leads and three chest leads (CF₁, CF₂, and CF₃) being employed. One case of paroxysmal auricular fibrillation in a woman of fifty-one years with no apparent structural cardiac disorder was found and this reverted to normal rhythm under the use of 0.4 gm (6 gr) of quinidine every two hours for five doses. One case of right-bundle-branch block was found in a man of forty-eight with no signs or symptoms of organic cardiac damage. The forty-three-year-old man with suspected mild coarctation exhibited a moderate degree of left-axis deviation with a low upright T wave in Lead CF₃ in the electrocardiogram. All the remaining tracings fell within the realm of normal.

For some time it has been shown by the anthropologists that most peoples of the New World have blood type "O" whereas Asiatics generally exhibit blood type "B". Therefore, it would be of great interest to know the blood types of the Aleut peoples, to achieve this aim one of the group, Dr William Laughlin, of the Peabody Museum, typed everyone included in the series. Table 3 gives the results. Of note is the fact that the New World probably

was the point of origin of the Aleutian Islanders before migration. This is substantiated by the low value of the subgroup "n". Dr Laughlin has also been utilizing a method to determine the blood types of skeletal remnants on all specimens brought back to Harvard's Peabody Museum, although a report cannot be given now it will probably be ready soon.

At present the health of the native Aleuts concerns chiefly the jurisdiction of the Alaska Native Service. Each island is visited by the Government health boat, the *Hygieia*, about once every year or two, depending upon the weather and so forth. During this time as much medical and dental work as possible is crowded into the ten days or two weeks spent at each village. The medical personnel aboard Coast Guard boats give readily of their time and facilities at whatever village they may happen to visit during their course of duty. The time spent at various islands is so short, however, that their work is restricted to the emergency category. The

TABLE 3 Blood Types and Rn Determinations among 117 Aleuts

TYPE	PERCENTAGE
O	49.5
A	44.7
B	4.5
AB	2.3
mn	69.8
mn	20.9
Rh—	100.0

Army and Navy installations have also been most generous with their aid to any Aleut requiring attention, although it is not their explicit duty to provide such care. Lastly, each Government school-teacher has been instructed in the general principles of first aid and has on hand certain of the more useful medications to treat the ill. However, all these measures seem inadequate when the end result is studied. The Aleut has not fared well with the introduction of the white man's culture and needs help desperately not only in organizing a social structure that can cope with the new problems and demands but also in preparing the proper environmental soil in which such a social reformation will thrive. The Aleut, for the most part, is also a spiritually ill person who needs the active guidance of some social or religious organization, Russian Orthodox faith or other, that will renew in him the spark of hope and the time-tested tenets of a good life.

SUMMARY AND CONCLUSIONS

Data on the present health status of 117 Aleutian Islanders are presented. The findings will be analyzed in subsequent reports.

In some parts of the world there no doubt live groups of people who exhibit the exact basic criteria

for an excellent control in many of the experiments of crucial value in present-day researches, and much can be learned by spending some time among these people, living close to them and observing their habits and customs so that progress in all fields of endeavor can be made. Such a variation of organized analysis and investigation has not to the present been utilized to its best advantage.

The introduction of the white man's culture in an area not properly receptive to the change because of a social and economic structure inadequate to absorb the impact can be definitely detrimental

to the persons involved. This has been the situation in the Aleutian area, and it will need to be amended before progress along any line of endeavor can be expected.

226 Marlborough Street

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SUPRARENAL HEMORRHAGE IN PREGNANCY*

Report of a Case With a Review of the Literature

G. ARNOLD, M.D.,† A. G. RICHER, M.D.,‡ AND J. J. LEPORE, M.D.§

FRAMINGHAM, MASSACHUSETTS

KEELE and Keele¹ made the first attempt to distinguish between the adrenal hemorrhage occurring in the course of septicemia, as in the Water-

house-Friderichsen syndrome, and the adrenal hemorrhage occurring independently of any infectious process, for which the synonymous terms of hem-

TABLE 1 Data in 19 Cases of Suprarenal Hemorrhage*

AUTHOR	CASE NO.	SEX	AGE	ADRENAL GLAND INVOLVED	PAIN	TENDERNESS
Gooden ² (1837)	1	M	yr 46	—	Epigastric very severe sharp	—
Arnaud ³ (1900)	2	F	17	—	Epigastric very severe persistent	Epigastric
Lavenson ⁴ (1908)	3	F	44	—	Epigastric severe	Epigastric
Hektoen ⁵ (1909)	4	M	?	—	Left costal margin right costal margin persistent severe	Under costal margins
Michaux and Marquet ⁶ (1923)	5	M	74	—	None	Under costal margins
Pearl and Brunn ⁷ (1928)	6	M	45	—	Right and left lumbar region severe persistent	Right and left costal margins
Barsom ⁸ (1936)	7	M	50	—	Diffuse abdominal severe persistent	Diffuse
Hall and Hemken ⁹ (1936)*	8	M	40	—	Left lumbar region very severe	—
Altschule ¹⁰ (1939)	9	M	72	—	Epigastric very severe persistent	Epigastric
Keele and Keele ¹ (1942)	10	F	32	Right	Below right costal margin very severe persistent	Below right costal margin
Williams and Ellis ¹¹ (1944)	11	F	23	Both	Lumbar region mild	None
Edelman ¹² (1945)	12	M	61	Right	Epigastric severe radiating to the right	Right upper quadrant
Dodds ¹³ (1945)	13	F	38	Both	Epigastric radiating mild	Right costal margin
Thorstad ¹⁴ (1942)	14	M	55	Right	Epigastric	None
Thorstad ¹⁴ (1942)	15	M	40	Right	Lumbar region mild	None
Oddo ¹⁵ (1946)†	16	F	36	Left	Left costovertebral angle severe lancinating	Left renal region
MacMillan ¹⁶ (1947)	17	M	60	Both	Epigastric and right upper quadrant, severe	Right upper quadrant
Burnett ¹⁷ (1948)	18	F	23	Both	None	—
Arnold, Richer and Lepore (1948)	19	F	22	Right	Right upper quadrant, mild, radiating to right flank	Slight

*An additional case is reported by the authors in an 18-yr-old girl in early pregnancy with severe hyperemesis and fatal bilateral adrenal hemorrhage.

*From the Division of Laboratories, Framingham Union Hospital.
†Assistant resident in surgery, Massachusetts Memorial Hospitals, Boston, Massachusetts.

‡Attending physician, Marlborough Hospital, Marlborough, Massachusetts.
§Attending surgeon, Marlborough Hospital, Marlborough, Massachusetts.

orrhagic suprarenal infarction, acute hemorrhagic adrenalitis, spontaneous suprarenal hemorrhage and suprarenal apoplexy have been suggested

Table 1, in which the pertinent data of the 19 cases of the literature (including the 1 presented below) are shown in comparison, reveals the condition to be twice as frequent in the male as in the female, without any apparent relation to age, the youngest patient being a girl of seventeen and the oldest a man aged seventy-four years. In 11 cases the site of the hemorrhage was the right adrenal gland, in 1 case the left and in 4 both adrenal glands were involved by the process. No information about the site of the lesion was given in the remaining cases. Considering that the right adrenal vein drains directly into the vena cava (the left goes to the left renal vein), it has been postulated that this is the reason for the more frequent involvement of the right adrenal gland.

As for the mechanisms underlying the process, in 6 of the 19 cases no cause was apparent. In 1 case the hemorrhage developed eleven days after a burn (Arnaud⁴). Trauma was obviously the factor in one of the 2 cases of Thorstad¹⁴ in which there

were cases of MacMillan,¹⁶ Edelman¹² and Michaux and Marsset.⁶ There was a history of questionable grippe in the case of Williams and Ellis.¹¹ A co-existent bronchiogenic carcinoma was present in the case of Altschule,¹⁰ but there was no evidence that the adrenal glands were the site of metastatic involvement. Pancreatitis was present in Lavenon's⁴ case, and the possibility cannot be ruled out that necrotic changes in the retroperitoneal fat had followed the development of this condition. In 5 cases, including the one presented below, the adrenal hemorrhage developed in the course of a pathologic pregnancy—a combination that makes one suspect something more than a mere coincidence.

CASE REPORT*

A 22-year-old primigravida was admitted to the Marlborough Hospital on October 19, 1947, because of pain in the right side of the abdomen, more accentuated at the right costovertebral angle.

The patient had first been seen by one of us (A.G.R.) 75 days previously, when she was 2 1/2 months pregnant. The blood pressure was 150/80, but except for slight intermediate morning nausea and some urinary frequency she had no complaints. She had had the usual childhood diseases without complications, and there was no history of previous hospital-

TABLE 1 (Continued)

CASE NO	RIGIDITY	TEMPERATURE °F	PULSE	RESPIRATIONS	BLOOD PRESSURE	WHITE CELL COUNT $\times 10^3$	DURATION	REMARKS
1	—	—	—	—	—	—	? mo	—
2	—	—	—	—	—	—	No of hr	Hemorrhage occurred 11th day after burn
3	Slight	95.0	120	45	—	5.2	36 hr	Patient also had pancreatitis
4	—	97.0	100	—	—	—	21 days	—
5	None	98.0	80	—	—	—	14 hr	Patient also had chronic nephritis
6	None	102.0	90	30	120/80	16.0	7 days	—
7	Slight	99.0	90	—	—	—	4 days	—
8	Perceivable	104.0 (2nd day)	—	—	—	—	2 days	—
9	Marked	98.0	104	32	140/95	20.0	10 hr	Patient also had bronchiogenic carcinoma
10	None	98.0	80	20	120/80	22.0	12 hr	Patient 8 mo pregnant
11	None	100.0	84	—	—	—	1 day	Patient had questionable mild grippe
12	None	99.2	100	—	140/80 200/98	5.2	6 days	Patient operated on 13 days after admission recovery. Arteriosclerosis of right adrenal gland.
13	None	98.6	80	—	136/86	26.9	1 day	Hemorrhage occurred 3rd day post partum
14	None	96.4	96	24	120/90	—	3 days	Patient had renal tuberculosis recent trauma right upper lumbar region
15	None	97.0	70	20	120/76	16.9	7 days	—
16	None	100.0	104	20	118/80	9.0	123 days	Patient recovered after operation
17	None	Normal	100	26	200/100	10.6	4 days	Patient had had hypertension for several years
18	—	—	—	—	Not obtained	—	2 hr	Patient 5 mo pregnant and 2 hr post abortion had threatened abortion at 1 mo
19	Sluggish	102.0 (3rd day)	120	Normal	160/70	12.0	7 days	Patient 5 mo pregnant with active bleeding from endometrial implants

*Probably the first successful operation (1936) for adrenal hemorrhage in an adult although report published later (1946) than that of Edelman¹² (1945)

was coexistent renal tuberculosis. A condition of long-standing hypertension, arteriosclerosis and chronic nephritis undoubtedly played a role in the

ization, accidents or injuries of any sort. The family history was noncontributory. Urinalysis was negative for sugar and

*The study of this case was made possible by Dr. C. G. Tedeschi, Director, Department of Laboratories, Framingham Union Hospital, to whom we express our appreciation.

albumin, the specific gravity was 1.024, and the sediment failed to reveal casts or cells. Nineteen days before admission she was seen again for a dull, intermittent discomfort in the lower back, accentuated by prolonged standing or walking and almost completely relieved by lying down. The blood pressure was 158/70, the temperature was 99°F, and the pulse 114. Urinalysis was negative. On the morning of October 17, on awakening from sleep, she had experienced an increase in the severity of the backache, accompanied by moderate urinary frequency and urgency. She attempted to do some housework but was unable to do so. She returned to bed and remained there for 24 hours with almost complete relief of back discomfort. Six hours prior to hospitalization she began to note abdominal pain that was maximum at the level of and to the right of the umbilicus. This shortly was accompanied by pain in the right costovertebral angle. Hospitalization was deemed advisable.

Physical examination revealed a patient who appeared ill and asthenic, was in obvious distress and complained of pain in the right flank and right middle portion of the abdomen. The skin and the mucous membranes of the lips and of the oral cavity were moderately pale. The abdomen was distended and tender in the right middle quadrant and right flank, with moderate spasm and rigidity in these areas. The uterus was enlarged to the level of the umbilicus. The fetal heart could not be heard. There was no evidence of vaginal bleeding, and rectal examination was negative.

The temperature was 100.2°F, the pulse 120, and the respirations 25. The blood pressure was 160/70.

Examination of the blood disclosed a red-cell count of 4,200,000, with a hemoglobin of 76 per cent, and a white-cell count of 12,050, with 76 per cent neutrophils, 20 per cent lymphocytes, 2 per cent monocytes and 2 per cent eosinophils. Urinalysis was negative.

With the preoperative diagnosis of acute appendicitis, the abdomen was opened through a right-lower-quadrant, pararectus incision. A large amount of serosanguineous fluid flowed from the abdominal cavity. The uterus was enlarged to the size of a 5 months' pregnancy. The appendix, when delivered into the wound, was normal. There was free oozing of blood from the right ovary, in which a number of raised, reddish nodules, suggesting endometrial implants, were visible. The oviducts and the left ovary were normal. The upper abdomen could not be examined owing to the pregnant uterus and the small size of the incision. The appendix was removed, together with small pieces of tissue from the bleeding ovary, and the abdomen was closed in layers with no drainage.

Pathological examination of the specimens showed the appendix to be normal, formations suggesting endometrial implants were recognized in the pieces of ovarian tissue. The patient continued to complain of pain in the right flank, and the abdomen became tympanitic and moderately distended. Penicillin and corpus luteum extracts were given. The temperature, pulse and respirations were within normal limits. The blood pressure was 140/60. On the next day the situation was unchanged. Examination of the blood on the third day showed a drop in both the hemoglobin, which was 67 per cent, and the red-cell count, which was 3,150,000. The urine was normal. In the meantime the temperature had risen to 102°F. The pain in the costovertebral angle had become sharp.

On the 4th day the condition became progressively worse. The abdomen was markedly distended, but there was no nausea or vomiting. The blood pressure had dropped to 134/60, and the red-cell count was 1,950,000, with a hemoglobin of 39 per cent. The patient was still rational and alert.

With the possibility in mind of an intra-abdominal bleeding, the patient was again operated on. Under nitrous oxide, oxygen and ether anesthesia a midline subumbilical incision extending right to the level of the navel was made. A large amount of serosanguineous fluid was free in the abdominal cavity. The implants on the right ovary had shrunk and now appeared as pale gray, slightly raised, flabby nodules. The left ovary was normal, and no change was noticed in the broad ligaments, oviducts or uterus. The left kidney was palpated and found to be normal. The right kidney, however, was encompassed by a semisolid mass, which extended from its lower pole up to the diaphragm, displacing the liver anteromedially. At this time the patient began to breathe laboriously, the pulse became rapid and feeble, and the blood pressure started to drop until it became unperceivable. All possible

resuscitation measures were applied without result, and the patient died.

Post-mortem examination* 2 hours after death revealed the body of a well developed, well nourished, extremely pale young woman. Except for the two abdominal incisions no external injuries or lesions of any kind were seen. The abdominal cavity was filled with a serous, sanguineous fluid in which a few blood clots were floating. The peritoneal membranes were blood tinged but smooth and glistening. The intestinal loops were inflated but otherwise not remarkable. The pregnant uterus, oviducts and ovaries were normal. The right kidney was encased by a large, reddish-brown, fluctuating mass, 20 cm long and 10 cm thick, of partly clotted and partly fluid blood. Section through this mass revealed a large, swollen, hemorrhagic adrenal gland, 7 cm long and 2 cm thick. It was ruptured at one pole and covered by a thick clot of blood. On section, the limits between cortex and medulla could hardly be recognized owing to infiltration of blood. Small islands of golden-yellow tissue, the size of a pinhead or a little larger and suggesting chromaffin tissue, were found adjacent to the ruptured pole of the gland. The other adrenal gland was intact, and none of the other abdominal organs showed changes of significance. The kidneys together weighed 280 gm, and except for a marked pallor neither appeared to be unusual.

Examination of the brain and organs of the chest was not permitted.

Microscopical examination of the right adrenal gland showed both cortex and medulla to be widely infiltrated by well preserved red blood cells, with almost complete obliteration of any normal structure. Large collections of polymorphonuclear leukocytes were noticeable here and there, most numerous in the proximity of yellowish-brown granules of hematic pigment, either free or in large macrophages. A middle-sized vein, close to the hilus, was found almost completely occluded by a recent thrombotic mass, which consisted mainly of blood platelets and of cellular debris imbedded in a structureless eosinophilic material. The vessel wall was swollen by edema and displayed moderate perivascular infiltration by granulocytic cells. The left adrenal gland was intact, and no significant deviations from the normal were shown by the sections from the liver, spleen, kidneys or gastrointestinal tract. No endometrial implants were revealed in the ovaries. The placenta showed small hemorrhagic infarcts.

DISCUSSION

From the study of the vascular supply of the adrenal gland in nearly 400 bodies Anson and his associates¹³ concluded that far more than the usual three arteries depicted in the standard textbooks—often as many as fifty—are present in each gland, all draining into a single vein. If this is the case one wonders why vascular accidents, followed by infarction of the gland, do not occur more frequently. It seems that both increased blood pressure and venous occlusion by the thrombus may have played equally important roles in causing the fatal hemorrhage in the case reported above.

It is difficult to conceive any correlation between the endometriosis and the adrenal hemorrhage, other than a coincidence.

A bearable, persistent pain, made worse by motion, and localized hyperalgesia characterized the onset of the condition in the case described above. As in those reported by others, absence of purpura, which is constant in the Waterhouse-Friderichsen syndrome, is a point of interest.

With the increased oozing of blood into the tissues of the perirenal region the signs and symptoms proper to intra-abdominal hemorrhage made their appearance. At this stage, the pain, which was

*Performed by Dr. C. G. Tedeschi.

mainly referred to the infarcted area, became sharp. Pallor and prostration and drop of blood pressure were signs of the impending collapse.

Inasmuch as adrenal hemorrhage, if left alone is fatal, the only choice is prompt recognition of the condition, followed by surgical intervention. If we had thought of this possibility and properly explored the adrenal regions at the time of the first operation, perhaps the patient's life could have been saved. This case strongly emphasizes the necessity of including adrenal hemorrhage in the differential diagnosis of any uncertain abdominal situation. If this will be kept in mind it is hoped that other reports of successful interventions will be added to the 2 cases so far reported in the literature.^{12, 15}

SUMMARY

A fatal case of intra-abdominal hemorrhage following infarction and rupture of the right adrenal gland in a twenty-two-year-old woman, in the fifth month of pregnancy, with a history of moderate hypertension, is reported. The death is explained by increased blood pressure, complicated by thrombotic occlusion of a relatively large venous branch of the gland. A condition of endometriosis in the

right ovary — a most extraordinary and misleading coincidence — was present. The 18 cases previously described in the literature are reviewed and analyzed.

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PROPHYLAXIS AND TREATMENT OF HEAT-REACTION STATES

LOUIS FRIEDFELD, M.D.*

NEW YORK CITY

DURING a severe heat wave in the summer of 1937, 8 of the aged residents of the Home of Old Israel in New York City succumbed in a single day under circumstances that left no doubt that the high environmental temperature was the precipitating cause of death. During the much more severe heat wave in August, 1948, not a single death occurred in the same institution although the mortality rate for the city as a whole was higher than that in 1937. It is believed that the reason for the difference is that the unfortunate experience of 1937 had led to more systematic prophylaxis and treatment of heat-reaction states. This paper presents a discussion of the methods followed since 1938 that have resulted in the striking reduction in the mortality from these conditions in the eleven succeeding years.

MAGNITUDE OF THE PROBLEM

None of the eight deaths that occurred on the fourth day of the heat wave in 1937 could have been anticipated on the basis of previous medical status, although most of the fatal cases occurred

in patients convalescing from infectious or vascular disorders. In several cases the immediate cause of death was heat stroke with hyperpyrexia, in others, heat exhaustion initiated a rapid downhill course. At the same time, other institutions in the metropolitan area had comparable experiences, and there was a sharp rise in the general mortality rate for the city of New York. Similar findings were reported from other cities.¹

Again, in the latter part of August, 1948, there was a severe and prolonged heat wave that affected a large portion of the country and contributed to a serious rise in the general and infant mortality rates. Although this did not approach the situation in Peking in July, 1743, when 11,000 persons are said to have perished on the streets from the effects of the heat,² New York City reported twice as many deaths for the week ending September 3 as for the corresponding week in 1947, or the preceding week in August, 1948 (Fig. 1). Table I shows the temperatures and deaths in August, 1948.

The importance of this heat-related mortality increase was further emphasized when it was noted that the last time that the weekly death rate had exceeded the expected death rate by over 100 per

*Adjunct in medicine, Beth Israel Hospital; chief of medicine, Home of Old Israel.

cent was in February, 1920, when the third wave of the devastating influenza epidemic of 1918-1920 hit the city

Forty-one homes for the aged in New York City, with a total census of 6688, responded to a questionnaire on the effects of the heat wave that began on August 23, 1948. The total deaths for the control period of August 11 to 20 were 25, whereas the deaths from August 21 to 30 rose to 68, an increase of 172 per cent. In the latter group 82 per cent occurred in the four days beginning with August 27, during which all the 14 cases of heat stroke also occurred. In 22 cases deaths were reported from other causes,

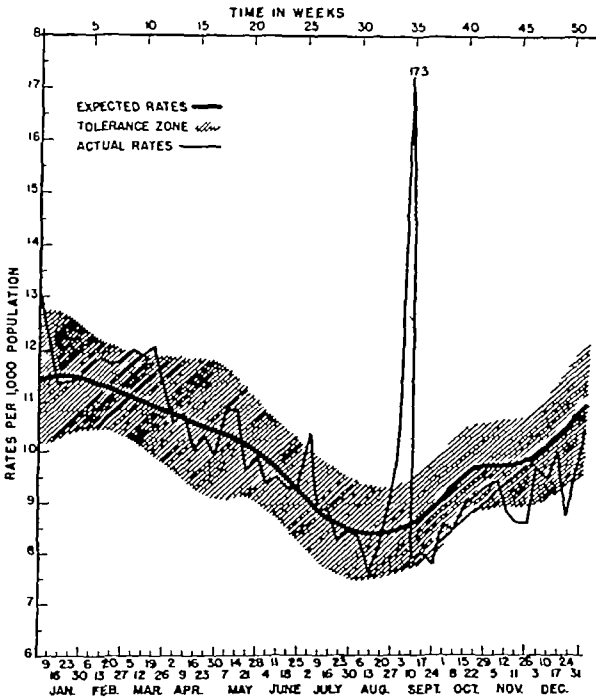


FIGURE 1 Deaths from All Causes City of New York, 1948 (Based on Data Supplied by Statistical Division, Bureau of Records and Statistics, Department of Health, New York City)

environmental heat effects contributing to the final outcome (Table 2)

After a study of the cases of heat reaction in 1937, a regimen was instituted at the Home of Old Israel for the prophylaxis and early treatment of these conditions. The results have been most gratifying, for there has been no recurrence of group deaths in the past eleven years, including the severe heat wave of 1948

TYPES

The symptom complexes that result from extreme summer heat are generally classified as heat cramps, heat exhaustion and heat stroke. In the condition known as "sunstroke," the clinical picture of either of the last two syndromes may appear. Heat ex-

haustion appears when peripheral circulatory failure due to vasomotor disturbance predominates, heat stroke results from the failure of the sweating mechanism through involvement of the hypothalamus, causing hyperpyrexia. Heat cramps do not terminate fatally, the mortality of heat reaction re-

TABLE 1 Temperatures and Deaths per Day, New York City, August, 1948

AUGUST	TEMPERATURES*		NO OF DEATHS†
	AVERAGE °F	HIGH °F	
15-22	—	—	192 (average)
23	74	82	197
24	77	85	196
25	80	91	240
26	90	101	281
27	90	99	446
28	90	99	567
29	86	93	587
30	80	87	390
31	71	79	247

*These are United States Weather Bureau readings recorded by a sheltered thermometer about 400 feet above street level at the Battery New York City. Exposed street readings are substantially higher.
†Based on data supplied by Statistical Division, Bureau of Records and Statistics, Department of Health, New York City.

sults from either heat exhaustion or heat stroke. The statistical breakdown between these two conditions seems almost impossible because of difficulties in diagnosis, the tendency to report pre-existing chronic conditions as the primary cause of death and the inclination to reject a diagnosis whose report would automatically result in a medical examiner's inspection.

Heat Cramps

Under normal conditions more than 95 per cent of salt is eliminated by the kidneys,³ but in heat cramps, the mildest of the heat-reaction states, there is a depletion of sodium chloride as the result

TABLE 2 Causes of Death for the Week Ending September 3, 1948, Compared to the Expected Average per Week for August, New York City*

CAUSE	WEEKLY AVERAGE FOR AUGUST	AVERAGE FOR WEEK ENDING SEPTEMBER 3
Cardiovascular renal	585	1364
Cancer	290	423
Diabetes	60	133
Pneumonia	35	129
Heat stroke	0	48
All others	330	580
Totals	1300	2677

*Based on data supplied by Statistical Division, Bureau of Records and Statistics, Department of Health, New York City.

of excessive perspiration. This is particularly common in an atmosphere of low humidity that facilitates the rapid evaporation of sweat.⁴ Excessive ingestion of water during periods of active perspiration may enhance this salt depletion by causing additional loss of salt in the urine. Low-salt diets,

diarrhea and diuresis also predispose to this condition. With acclimatization, the salt content of the sweat is reduced.⁵

In heat cramps there are painful contractions of the voluntary muscles of the extremities and the abdominal wall.⁶ Nausea and vertigo may be present. This condition can be prevented by the prophylactic ingestion of salt, or corrected readily by removal of the patient from the hot environment and administration of saline solution by the oral or intravenous route. There is no elevation of body temperature and no significant mortality.

Heat Exhaustion

During heat exhaustion, in addition to heat cramps, there may be peripheral circulatory collapse, nausea, vomiting, scanty urine, headache, giddiness and anorexia. Profuse sweating and sodium depletion are contributory factors. The skin may be cool, moist, pale or cyanotic.⁷ Body temperature may be normal, slightly elevated or slightly lowered. In previously normal persons there is generally no direct mortality, especially if the patient is removed from the excessive environmental heat. However, in the aged or those suffering from infections or chronic debilitating diseases, there may be a significant rise in the mortality rate that would commonly have been attributed to the pre-existing condition. This may account for the drop in the general death rate in the weeks following a heat wave (Fig 1). Many of the patients who succumbed during the period of excessive heat included those suffering from diseases that would ordinarily have been listed in subsequent death reports. Susceptibility to heat exhaustion varies with physical condition and the presence of alcoholism, but the aged are particularly vulnerable, especially those who suffer from debilitating diseases or circulatory impairments⁸ (Table 2).

Heat exhaustion may be prevented or controlled by limited exposure or exertion in high environmental temperatures, adequate hydration and an increased salt intake. The amount of salt depends upon the condition of the patient, the degree of excessive perspiration and the ability to restore an output of at least 30 ounces of urine. Although an increased daily ingestion of 5 gm of salt ordinarily suffices, in extreme cases the need may rise to 50 gm a day. In the active treatment of heat exhaustion, aside from removal of the patient to a cool place and administration of salt and water, specific treatment may be indicated to combat a state of shock.^{9, 10}

Heat Stroke

Heat stroke is an acute disease due to prolonged excessive environmental temperature causing a derangement of the heat-regulating center of the hypothalamus, and characterized clinically by the cessation of sweating, hyperpyrexia and central-

nervous-system disturbances. This is the most serious of the heat-reaction syndromes, and may be solely responsible for mortality directly caused by excessive environmental heat in previously normal persons. It is also known as heat hyperpyrexia. Watts¹¹ was among the first to note that the body temperature was elevated in major heat affections. Salt depletion is not an important factor in this condition, which is even more likely to appear when high humidity reduces the degree of body heat dissipation through lessened sweat evaporation. The sudden cessation of sweating is the important premonitory sign,¹² and the lesser heat syndromes need not coexist. The importance of the cessation of sweating is appreciated when it is recalled that this is the sole method of heat dissipation when the environmental temperature exceeds 95°F,^{13, 14} and that in the evaporation of 1 liter of sweat, 580 calories are absorbed.¹⁵ Conduction, convection and radiation, which perform 70 per cent of this function at ordinary temperatures, are no longer effective.^{16, 17}

After several days of extreme summer heat there is a sudden cessation of sweating — a premonitory sign that warrants emphasis. Although there may be increased urination, headache, weakness, nausea or faintness, the clinical condition may be precipitated with sudden collapse and coma. Unless shock is present, the skin is hot, dry and flushed. The body temperature rises sharply and may exceed 106°F. There may be convulsions, cyanosis, vomiting, incontinence, delirium or stupor. Although tachypnea is noted at first, Kussmaul breathing may supervene, and the Cheyne-Stokes type of respiration may be preterminal. Patients who remain ambulatory commonly have a staggering gait. There are difficulties in speech or swallowing, along with dryness of the mouth and excessive thirst. Lower-nephron nephrosis has been reported.^{18, 20} Persisting coma or delirium has grave prognostic significance.²¹

The mortality rate due to heat stroke is high, particularly among infants, the aged, those suffering from infections or chronic debilitating conditions,²² and those engaged in physical activity while exposed to excessive environmental heat. In a large series of patients admitted to a general hospital with heat stroke, the mortality was 44 per cent.²³ In the aged the rate is significantly higher. Most of the cases begin to appear about the third or fourth day of a heat wave. After the cessation of sweating and the onset of hyperpyrexia, over 70 per cent of patients die in less than twenty-four hours.⁶ Mortality figures for white people are many times higher in the North Central states than in Florida,²⁴ but this may be due to the effect of seasonal variations on acclimatization.²⁵ Although Negroes appear to be more vulnerable than white people, and males more often affected than females, occupational activities and outdoor exposure may account for these differ-

ences It is significant that half the deaths from this cause in the United States have occurred in persons over sixty years of age, whereas 45 per cent, the highest in any single year, occurred below one year of age The factor of individual susceptibility must also be considered

In the genesis of heat stroke, prolonged exposure is more important, to an extent, than the degree of elevation of environmental temperature This may be related to a suggested cause of heat stroke, such as exhaustion of the heat-regulating center of the hypothalamus^{12, 26, 27} After recovery from one attack of heat stroke an increased susceptibility to recurrences remains²¹

PROPHYLAXIS AND TREATMENT

During the 1937 period of extreme summer heat, the significance of the premonitory cessation of sweating in the development of heat stroke was apparent As a result, the early detection of this sign became an important part of the regimen that was instituted for the management of the aged Although some deaths still occurred among persons debilitated by severe infections or degenerative disorders, the frequency was greatly decreased, and deaths due to heat stroke among the physically well in the aged population were practically eliminated

Heat-Wave Regimen

In this heat-wave regimen, light, airy clothing is distributed, frequent bathing and proper skin hygiene are encouraged, physical exertion and prolonged outdoor exposure during midday are discouraged, rest periods in well ventilated rooms are arranged, a light diet with increased carbohydrate and decreased protein is prepared, salted foods are added to the diet and salt tablets distributed at regular intervals, plenty of drinking water and citrus-fruit juices are made available, supplementary vitamin preparations are furnished, and sweat rounds are conducted

Sweat rounds have been a significant feature of this program, even as the use of an oxygen tent has been most helpful in the treatment of these cases Several times each day the resident staff routinely inspects all the aged in hospital quarters, as well as those reported ill among the ambulatory This searching out of the characteristic premonitory sign has been helpful in permitting early therapy in heat stroke

When a dry skin is noted, even though the body temperature is normal and there are no associated symptoms, the patient is put to bed and clothing is removed Since air-conditioned rooms are not available at the institution, sponge baths are given frequently, and fans are used to maintain air circulation The increased drinking of water and ingestion of salt is encouraged When necessary, salt solutions are administered intravenously

If sweating does not return in a short while, or if fever is present, the patient is placed in an oxygen tent Here the air is cooled to below 50°F, air motion is maintained, and low humidity levels are obtained The increased oxygen tension also is helpful because of the marked rise in metabolism Generally, this treatment suffices However, if hyperpyrexia supervenes, the patient may be wrapped in cold wet sheets or sprayed from a water nozzle, and fans directed against the body surface¹ Iced tub baths may be used,²⁸ but shock and death have resulted from this drastic procedure In the latter method, the skin must be massaged while the patient is in the tub This friction maintains the skin hyperemia, otherwise the overheated blood would be driven to deeper areas⁹

The control of the central-nervous-system symptoms and the lowering of the temperature, along with the reappearance of sweating, are hopeful prognostic signs However, even after sweating is restored and the temperature returns to normal, relapses may occur¹² If sweating returns but fever continues, an intercurrent complication is to be suspected

SUMMARY

Significant morbidity and mortality result from prolonged exposure to extreme environmental heat Heat cramps, heat exhaustion and heat stroke are described The differences in the therapy of heat exhaustion and heat stroke are considered The importance of sweat rounds is discussed in a regimen for the prophylaxis and treatment of the hyperpyrexia

It is pointed out that cessation of sweating is a highly characteristic premonitory indication of the onset of heat stroke During heat waves, careful observation of patients in a home for the aged for the early detection of this cessation of sweating and the immediate institution of appropriate therapy have enormously decreased the incidence of mortality due to heat stroke The benefits derived from the early use of an oxygen tent are described

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MEDICAL PROGRESS

PREVENTIVE MEDICINE*

MIRIAM D MANNING, M D †

BOSTON

SEVENTEEN centuries ago Aretaeus¹ of Capadocia made the first mention in formal medical literature of the practice of isolation as a means of controlling disease, and until recently the control of communicable disease has been the prevailing and only concept of preventive medicine. If one studies the history of preventive medicine the reason for this concept is obvious, but if the new accomplishments in the field are to be placed in their proper perspective, the first realization must be that not the least of the recent advances has been recognition of the profound proportions and province of preventive medicine.

Simmons,² although recognizing Smillie's differentiation between public health and preventive medicine (namely, that preventive medicine is an individual responsibility and public health a community one), comes to the wise conclusion that these inevitably overlap and that the final responsibility rests with the medical and allied professions. He defines preventive medicine as "the sum total of all those services required to prevent disease and keep well people well." Armstrong³ has said "preventive medicine is not a specialty, but an attitude." Galdston⁴ believes "the term preventive medicine is self-limiting in the adjective preventive." Smith and Evans⁵ give the following definition "the intervention of the physician or his technical allies in a limited range of situations in which specific diseases can be warded off or specific deterioration of the patient's condition can be forestalled." They take the broad view that preventive medicine has

a definite responsibility to prevent preventable disease, prevent the consequences of curable chronic diseases, and prevent or delay the consequences of nonpreventable, noncurable diseases.

Consideration of these definitions makes one believe with Stieglitz that preventive medicine is thus an integral part of the practice of medicine and has its function in all stages of the patient's existence, from the period of "preconception" to advanced age.

As a tribute to the oldest and still most active field in preventive medicine, advances in the control of communicable diseases are considered first.

COMMUNICABLE DISEASE

Significant increase in diphtheria morbidity in several states shows that immunization in childhood does not provide lifelong security, and that diphtheria is not a disease of infancy and childhood only. Eichelberger⁶ reports that 21 per cent of the cases reported in 1946 occurred in the age group ten to nineteen years. In a study of high-school groups in New York City he found that of previously immunized pupils, 20 per cent in junior high, and 18 per cent in senior high school were Schick positive.

Schick testing of American troops in Europe showed that 30 per cent of the persons under thirty-five years of age were Schick positive or combined reactors.⁷ (The reliability of the Schick test as a measure of immunity, although open to question, is at present the best means for mass determinations.) As a result of studies showing that diphtheria is becoming relatively more prevalent in the older age groups, and that childhood immunity does not

*The Prize Essay for 1949
†Formerly fourth year medical student Tufts College Medical School

last a lifetime, it is recommended that booster doses of 0.5 cc of diphtheria toxoid be given to Schick-positive reactors in the age group from ten to nineteen years. Whereas adults do not tolerate alum-precipitated toxoid well, persons in this age group showed no untoward reactions in the study made by Eichelberger.

The use of triple antigen as described by Sauer⁸ is one of the most recent contributions to childhood immunization. He obtained excellent levels of immunity to diphtheria, tetanus and pertussis by administering triple antigen — diphtheria and tetanus toxoids (refined) and pertussis vaccine (alum-precipitated) — after the sixth month of life. Alternate gluteal areas were used, and alum abscess almost completely eliminated when each deeply administered dose was terminated with 0.1 cc of air, and the site gently massaged.

The Chicago Pediatric Society⁹ recommends the schedules of active immunization shown in Table 1.

The Chicago Pediatric Society presents the following suggestion for passive immunization: diph-

theria, antitoxin (10,000 units) in known exposure of nonimmunized person, pertussis, human pertussis hyperimmune serum (20 cc) or hyperimmune globulin (2.5 cc) promptly when indicated, as in known exposure of nonimmunized infant or frail child (dosage as recommended by manufacturer), tetanus, antitoxin (5000 units), promptly administered in the nonimmunized after an injury that might lead to tetanus infection (subsequent immunization with tetanus toxoid is recommended), and measles, human serum globulin for modification or prevention when indicated, dosage recommended by manufacturer being used.

From a study by Banton and Miller,¹⁰ it appears that people should receive maintenance doses of tetanus toxoid as well as primary immunization and emergency injections when injury occurs. There is evidence that definite protection lasts for five years, but study of residual titers shows that periodic booster doses should be given for maintenance purposes every three or four years.

The study demonstrated that this maintenance dose may be more important than the booster dose at time of injury since many deaths from tetanus occur within four days of date of injury.

Press¹¹ has expressed the following opinion in immunization against tetanus:

active immunization against tetanus as a practical public health measure is indicated. Until further information regarding the pathogenesis of the disease or a simple method of estimating the natural antitoxin level is available, it should be given routinely by private physicians, and should be included in health department programs for children.

The toxoid may be given with diphtheria toxoid, or pertussis vaccine, or combined with the two.

It is important that this routine immunization be done because as Press¹¹ points out, 50 per cent of the injuries leading to tetanus in the civilian population are either so inconsequential as to be entirely unknown or exceedingly trivial. Also, tetanus bacilli are widely distributed, more being found in human feces than that of horses, so that

TABLE 1 Schedules of Active Immunization

AGE OF CHILD	SCHEDULE A	SCHEDULE B	SCHEDULE C
3 mo	Triple antigen (slow absorbing)	Pertussis vaccine (slow absorbing)	
4 mo	Triple antigen (slow absorbing)	Pertussis vaccine (slow absorbing)	
5 mo	Triple antigen (slow absorbing)	Pertussis vaccine (slow absorbing)	
6 mo	Triple antigen (slow absorbing)	Pertussis vaccine (slow absorbing)	Triple antigens (fluid or slow absorbing)
7 mo	Smallpox vaccination	Diphtheria and tetanus antigens (fluid or slow absorbing)	
8 mo		Diphtheria and tetanus antigens (fluid or slow absorbing)	Triple antigens (fluid or slow absorbing)
9 mo		Diphtheria and tetanus antigens (fluid or slow absorbing)	
10 to 12 mo		Smallpox vaccination	Smallpox vaccination
2 yr	Booster dose of triple antigen (fluid or slow absorbing)	Booster dose of triple antigen (fluid or slow absorbing)	Booster dose of triple antigen (fluid or slow absorbing)
5 yr	Booster dose of triple antigen (fluid or slow absorbing)		

the automobile age is no excuse for lessening our vigilance. Also, recognition of the undesirability of sensitizing people to horse serum that may be caused by the prophylactic use of tetanus antitoxin makes it more desirable to have a previous immunity that can be boosted by another dose of toxoid, which rarely has untoward reactions.

Mention of serum and globulin in immunization brings to mind the tremendous recent contributions made to preventive medicine by establishment of blood banks by hospitals, the American Red Cross and state departments of health. State and hospital services now provide for prenatal examination of blood for the Rh factor, the continued research and the development of facilities for the prevention of erythroblastosis fetalis due to this factor are a magnificent recent advance in preventive medicine.

The widespread use of blood and its derivatives has also presented problems that are now on the way to solution. Homologous serum jaundice and

infectious hepatitis have been recognized as two distinct diseases, varying in incubation period and mortality rate and possessing no cross immunity. Homologous serum jaundice is transmitted by blood and serum, and since there are no laboratory tests for detecting virus SH in plasma and serum, it is recommended that the practical and safe method of routine exposure to ultraviolet rays be made under properly standardized conditions. This causes no change in serum proteins except for a slight decrease in prothrombin and complement, and it inactivates the virus of serum hepatitis.¹² It is also a good idea to keep plasma pools as small as possible.

Since infectious hepatitis can be transmitted by yellow-fever vaccine and dehydrated, liquid and frozen plasma, as well as by flies, food, filth and contaminated water, the ordinary and well known hygienic precautions will prevent its spread. Also, gamma globulin, 300 mg per kilogram of body weight, will prevent an attack if given to an exposed person before the prodromal symptoms occur.

One of the most spectacular recent accomplishments in preventive medicine is immunization against tuberculosis with BCG. This vaccine has now begun to overcome the unfortunate publicity of the Lubec disaster, and is taking its rightful place, with isolation of open cases, as a major tool in the prevention of tuberculosis, which still ranks seventh in the causes of death, and is first cause in the young adult age group.

According to Birkhaug¹³ there are in the United States at the present time almost 180,000 cases of frank tuberculosis left at large to infect the healthy population.

Rosenthal and his co-workers¹⁴ in Chicago, after ten years' experience with BCG, confirmed the fact that vaccination with BCG (an avirulent and benign bovine tubercle bacillus, the bacillus of Calmette-Guérin) inhibits primary tuberculosis in a manner analogous to the specific resistance induced by spontaneous and clinically silent infection with virulent tubercle bacilli.

Heimbeck¹⁵ states that in a group of student nurses working in the tuberculosis wards, victims of the disease were nearly always among the negative tuberculin reactors, and Madson,¹⁶ of Norway, believes that the primary tuberculosis complex produced in negative reactors by BCG vaccination is sufficient to protect against progression of a subsequently superimposed virulent infection. Norway, in 1947, made BCG vaccination compulsory for all persons under fifty years of age. The experience of Holm¹⁷ has been that morbidity and mortality among children in a tuberculous environment has been reduced, after vaccination, to almost zero. He believes BCG to give considerable if not absolute protection.

The BCG Advisory Committee of the State of New York made the statement that BCG

vaccination is the only known practical method of reducing mortality from tuberculosis.

It must be mentioned that the favorable comments on BCG are based on the premise that a positive tuberculin test offers more protection than a negative test — a fact still open to question among authorities. The present opinion of the medical profession is that until further work is done, BCG vaccination should be reserved for negative reactors who are constantly exposed to tuberculosis, such as doctors, nurses, attendants and students.

The development of BCG does not in any way lessen the necessity for diligently pursuing the course of case finding and isolation that has helped bring tuberculosis down from its place in 1900 as first among the leading causes of death.

As an aid in case finding, the detection of tubercle bacilli by fluorescent microscopy may shorten the time necessary to examine a slide, and may in time prove more accurate than the Ziehl-Neelsen staining method. It is valuable at present in screening tests, the standard Ziehl-Neelsen procedure being reserved for questionable fluorescent slides.¹⁹

Despite the enormous amount of publicity and immense sums of money spent in research, the problem of poliomyelitis remains unsolved at the present time. Recently, however, there has been a saner approach to its epidemiology. It is the consensus at present that it is not necessary to close churches, schools and movies, but places where children come in close contact with each other, such as swimming pools and playgrounds, should be closed. Activities leading to unusual fatigue should be avoided during epidemic time. Patients with poliomyelitis can be admitted to the wards of general hospitals if adequate precautions are carried out.²⁰ Control of flies is probably of value, but mass spraying of towns with DDT is not warranted in the light of present knowledge. The virus of poliomyelitis has been isolated in both the respiratory and gastrointestinal tracts of human beings, and close contact between human carriers plays an important part in transfer of the infection.²¹

The use of massive doses of penicillin in the treatment of syphilis and gonorrhea is well known and is making case finding an even more effective means of controlling these diseases. Another step forward is the prevention of congenital syphilis by treatment of the mother, early in pregnancy, with penicillin varying from 2,400,000 to 4,000,000 units and following the dosage with careful quantitative serologic titers.¹² Penicillin can be given as late as the seventh month with effect if the infant is viable at the time. Relatively small doses must be given at first, with careful follow-up study, if the Herxheimer reaction is to be avoided. If this is done there is little danger.

In the control of venereal disease considerable progress has been made in the field of education. The available clinics for treatment have been made

known to people, and at the same time the finger of scorn has been removed from those who come for help. The Army made a notable advance along this line when it recently removed the penalty involved when a soldier reported a case.²³

The morbidity and mortality rates of the armed forces for diseases endemic in war theaters represents an advance in preventive medicine so comprehensive as to be beyond the scope of this paper. However, a few accomplishments must be mentioned. One of these is sanitary control of environment by the use of DDT and its derivatives. It was discovered in Europe and the Pacific²¹ that in spite of being adequately vaccinated, men suffered from diseases diagnosed as typhoid and paratyphoid fever when sanitation broke down or when they ate raw vegetables from native fields heavily fertilized with human feces. This emphasizes the fact that preventive medicine is the dual responsibility of those who control the environment and those who seek to increase individual resistance and immunity.

The value of atabrine is now well known, but the important lesson to bear in mind is "that malaria can be controlled anywhere in the world, in any environment, when trained personnel are given the necessary supplies and authority."²⁵ Preventive medicine may sometimes evoke the same high pitch of enthusiasm that war does, and the combined efforts of research, education and action may bring about equally excellent results in the control of disease in civilian populations.

The streptococcal group of diseases has been the subject of considerable investigation. Lemon²⁶ has found that, "Chemotherapy with sulfadiazine (in the absence of resistant strains) or penicillin, newer techniques of environmental dust control with oil and air sanitation using germicidal vapors have been shown to have definite value in reducing possibilities for cross infection offered by nasal streptococcal dispersers."

The routine use of scarlet-fever immunization is not necessary, and it should be reserved for persons needing special protection, and for institutional precautions. Scarlet fever at present, for unknown reasons, is a mild disease, and preventive medicine is wisely engaged in seeking the relation of scarlet fever to possible sensitization with the hemolytic streptococcus.

Rheumatic fever is now being given the emphasis it deserves. Griffith²⁷ has recently pointed out that tuberculosis, syphilis and rheumatic fever remain the most important infectious problems in America. Whether one believes the disease to be infectious or allergic, or both, the fact is that rheumatic fever is still the leading cause of death (except for accidents) among persons five to nineteen years of age. It causes countless cardiac cripples in an age group in which inactivity is particularly

frustrating and economic insecurity especially depressing. So little is known concerning the disease that the only recent effective methods of control have been through organized community effort. Griffith²⁸ has suggested a pattern of study similar to the Framingham tuberculosis demonstration, in which objectives are outlined and public co-operation obtained for a specific program. He bases these ideas on the belief that rheumatic fever is a contact disease and that its epidemiology is the epidemiology of the Group A hemolytic streptococcus.

Experiments with groups of children suffering from rheumatic fever have shown fewer exacerbations of the disease in youngsters treated with prophylactic doses of sulfonamides the year around. The prophylactic use of penicillin preceding oral surgery in patients with rheumatic fever has prevented the occurrence of subacute bacterial endocarditis. The status of the sulfonamides, however, is not sufficiently established for prophylaxis to be made a routine procedure.

Some of the devastating effects of unknown heart disease in patients with mild unrecognized rheumatic fever, as well as those having congenital anomalies amenable to cardiac surgery, may be prevented if attention is paid to the results of mass x-ray study. In heart disease as well as in tuberculosis the development of technics for routine inexpensive mass x-ray examination of the population has made possible the detection of early lesions. Photofluorography has been a satisfactory means of suggesting cardiac abnormalities to be diagnosed by further clinical study. Berenson²⁹ states that these abnormalities should be looked for in all routine x-ray films, and his series suggests that the number of persons with demonstrable cardiac abnormalities on routine fluorograms is greater than that of patients with tuberculosis in a given population, and that incalculable gains can be made when unsuspected heart disease is diagnosed.

INDUSTRIAL MEDICINE

Industrial medicine, which has led in programs of preventive medicine for adults, has a particular responsibility and opportunity to carry on the health education of adults. The accomplishments in this early field of endeavor are well known, but recent recognition of the fact that chronic illness and impaired efficiency due to lack of optimum health of the employee are an important cause of low production and increased operating expense has led to increased emphasis upon attention to minor illnesses to prevent their becoming serious. "In general the frequency of impairment, as measured by reduced effectiveness, is in inverse proportion to the severity."³⁰ Though the incentive for industrial medicine has been largely a mercenary one, results have been excellent.

MATERNAL AND CHILD HYGIENE

In the field of maternal and child hygiene preventive medicine has made some of its greatest contributions to medical progress. The health and nutrition of the mother during pregnancy have been given considerable study.

Dietary deficiencies have been found to increase the incidence of miscarriages, premature births and stillbirths, and functionally immature infants may be produced by mothers with an inadequate diet during pregnancy.³¹ Wesselhoeft³² has shown that rubella during early pregnancy is a severe hazard to the unborn child and is a problem deserving national investigation and public support, as well as international research.

Early recognition and surgical correction of congenital defects, properly isolated and equipped facilities for the care of the premature infant, and more rigid control in the nursery all are factors in the continued decline in infant mortality.³³ Early ambulation of the mother has prevented many of the unfortunate sequelae of childbirth.

A specific virus has been found for five epidemics of diarrhea of the newborn, but a virus etiology cannot be assumed for a particular epidemic unless the diagnostic work has been carried out by experts. Regardless of the etiology, the fecal-oral route is the usual one causing outbreaks of infant diarrhea in nurseries, and at present the only method of prevention is scrupulous attention to the already well known nursery and formula-room technics. Strict aseptic technic may block the spread of virus as well as bacterial organisms, and the results in many hospitals have shown that by careful observance of rules epidemics can be prevented in spite of the personnel shortage and overcrowding.³⁴

Wise retreat may represent an advance. An example is the return to breast feeding, "demand" feeding and "rooming in"³⁵ that make the present-day baby luckier than his brother born ten years ago, when any resemblance to the normal mother-child relationship was purely coincidental.

Prophylaxis against allergy in children is possible according to Shulman.³⁶ He believes that a minor sensitization in a child can set off an extensive chain of symptoms, and that every precaution should be taken in infancy to defer upset of allergic balance in the potentially allergic person.

A program calls for no major deviation from generally accepted practice in infant care. All that is necessary is a knowledge of the infant's inherited allergic tendencies together with an awareness of the relative allergic potencies of each of the major foods and inhalants.

Two thirds of the cases of bronchiectasis develop in the first two decades of life, and much of the prevention lies in the hands of the pediatrician. Lobar and lobular atelectases lay the foundation for the development of bronchial dilatation by destruction of the bronchial wall. If bacterial pneumonias are

diagnosed early and adequate chemotherapy given, and if areas of atelectasis that follow pneumonias and acute respiratory infections are re-expanded promptly, especially in children, much bronchiectasis can be prevented. The immediate removal of foreign bodies and benign endobronchial tumors is another important preventive measure.³⁶

An outstanding contribution to preventive medicine for children has been made by the dental profession. The topical application of sodium fluoride to the teeth of children, when done under dental supervision, is effective in reducing dental caries. The United States Public Health Service has set up units all over the country to show the efficacy of this now proved remedy. The American Dental Association has given its approval with the statement "Fluoride therapy should be used routinely in private dental offices and in school and community health programs." The Dental Section of the American Public Health Association has gone on record as endorsing and encouraging the development of effective methods for making this service available.

GERIATRICS

From the enticing prospects of pediatric preventive medicine one must turn to the rapidly growing and newer field of geriatrics. Advances here have been concerned with the problem of preventing or delaying the consequences of the nonpreventable, noncurable diseases. These diseases — heart disease, cancer and nephritis — are the three leading causes of death and, together with cerebrovascular accidents, the fourth cause, represent the etiology of much of the disability of the aged and aging. At the present time one cannot do a great deal to prevent or cure these diseases, geriatrics is making most of its progress by teaching people how to live with, and within, their physical limitations. Arthritis, eye changes and mental hygiene have recently received the attention of the Indiana State Board of Health.³⁷ The New York State Department of Health gave up its entire June, 1948, issue of *Health News* to "Problems of the Aged." Massachusetts is devoting time and money to the problems of cancer, diabetes and other diseases of the aged. Recreation departments are beginning to realize that programs for persons over sixty-five are a part of their work, and many cities are establishing places of meeting and giving encouragement to clubs that will give happiness and contentment to those no longer in active work. The object of geriatric medicine is to add breadth and depth, rather than mere length, to life,³⁸ and most of its progress thus far has been in laying the unspectacular but necessary foundations.

One of the major tasks of preventive medicine is the maintenance of physiologic tone in the hope of delaying, mitigating or if possible preventing the degenerative and senescent changes that account for most diseases in later life. One of these diseases

is cancer, and an organized battle against this has begun on all fronts—epidemiologic, research and administrative. The adoption of the Papanicolaou technic for the cytologic diagnosis of cancer of the cervix, lung, prostate and stomach has decreased the mortality. The advantage of this technic is that it makes diagnosis possible in the early stage while surgery is still of use, stained smears often showing malignant cells before any symptoms are evident. The number of false-positive reactions is few, and the incidence of correct diagnoses ranges from about 85 per cent in cervical cancer³⁹ to 64 to 90 per cent in cancer of the lung⁴⁰. The Mayo Clinic has had some success with the identification of malignant cells in the urine by the use of the Papanicolaou method⁴¹. As yet, there are too few trained workers in this field, which is one of the newest and most promising in preventive medicine. State health departments are beginning to realize that the chronic diseases of middle age may be studied by epidemiologic methods, and until the etiology is known they will have to be attacked on the administrative rather than on the purely scientific front.

ACCIDENT PREVENTION

It does no good to save persons from death by disease, only to have them die from accidents. The National Office of Vital Statistics⁴² states, "Deaths from accidents among children five to nine years of age were three times as great in 1948 as the combined number of deaths from poliomyelitis, and pneumonia, perhaps the most feared of childhood diseases." Accidents now are fifth in the leading causes of death, and until they are removed from this position, must be considered a serious threat to the health of the nation. The medical profession through national, state and local associations has recently become aware of this problem, and is making a determined aid to effect accident-prevention programs. In the age group from ten to fourteen years accidents outranked diseases of the heart, the single greatest nonaccidental cause of death, nearly 5 to 1. Even among young persons in the group in which tuberculosis is the leading cause of death, with heart disease and pneumonia next in line, accidents accounted for nearly twice as many deaths as the three together.

NUTRITION

The relation between food and preventive medicine is an ancient one. The Laws of Moses and Aaron⁴³ recognized that food may be a source of infection. The British Navy, in 1795, included lime juice in its rations, for the prevention of scurvy. Advances in food sanitation and vitamin requirements are beyond the scope of this paper, but the work of Schneider⁴⁴ in nutrition and natural resistance to infectious disease must be mentioned. He has localized, but not isolated or identified, in the

germ of whole wheat, a new nutritional entity. This agent has been responsible for the increased survivorship in specific breeds (host-genotype) of mice exposed to varying virulences (pathogen-genotype) of typhoid. Dr. F. J. Stare has called this work the highlight of the 1948 Food and Nutrition Section meetings of the American Public Health Association.

The fact that good nutrition not only prevents disease but also is responsible for positive health has long been known. Positive health, not merely the absence of disease, is the most recent and highest objective of preventive medicine, and notable scientific achievements have been made in the field of optimum nutrition. One might reasonably expect, therefore, a population in positive nitrogen balance. Unfortunately this is not true. The gap between what is known and what is done is widened by educational and economic problems that are not so easily solved as the equations of biologic oxidation.

MENTAL HEALTH

Although preventive medicine has made remarkable progress in all lines of endeavor, its most significant advance in recent years has been the attention that it has given to mental health. Modern society demands that its members live under a tension that is overwhelming, and many have failed to keep the pace required. As standards of living have improved, the need for psychiatry has increased. This is especially true in the very early and very late years of life.

The need of the child for help in adjusting himself to disturbing family situations and the high speed of life in general is being met by the work of such organizations as the Judge Baker Foundation and the James Jackson Putnam Children's Center in Boston, The Philadelphia Child Guidance Clinic, The Langley-Porter School in San Francisco, the Orthogenic School in Chicago, and the Rochester Child Health Institute in Minnesota. These centers not only offer help to the unadjusted child, and thus prevent mental ill health in later life, but also provide training centers for professional personnel. Their aim is preventive psychiatric and "well child" service. Another outstanding advance in this field is the formation of the Association of Psychiatric Clinics for Children, with Dr. Frederick H. Allen as president. Much of the prophylaxis of mental sickness begins in childhood, and the value of child psychiatry in preventive medicine is just now being realized. Dr. Allen⁴⁵ says, "The future of this all-important field is full of promise."

There is also the inevitable relation between physical and mental health. Psychosomatic medicine may well be considered a recent advance in the field of mental hygiene. "Physiological tone is so intimately connected with emotional balance that dynamic psychiatry is an indispensable tool of preventive medicine."

EDUCATION

The recent scientific advances in preventive medicine have put an additional burden upon the doctor, for as Clark⁴⁶ says, 'it is safe to say that at least three-fourths of the preventive work made possible by present day medical science must be carried by the practicing physician.' Have there been advances in methods of helping the physician to meet this increased responsibility? I believe there have been. Preventive medicine has been recognized as a logical and important part of the medical-school curriculum. Smith and Evans⁵ have outlined the work of the department of preventive medicine as follows: to teach the medical student what he needs to know about available technics for the prevention of communicable diseases, to give him understanding of epidemiology, and quantitative methods in medical science, to sensitize him to opportunities for arresting the development of noncommunicable disease, to make him aware of the patient as a person and thus to initiate him more fully into the art of medicine, and ultimately to show him how medicine can help to maintain or increase productive energy in both normal and handicapped persons.

These ideals of education will enable the physician to lessen the gap between what the scientist has discovered and what the people know and do. This is a difficult task. It is easier to vaccinate than to educate, but as surely as vaccination overcomes smallpox, education will overcome the ignorance that makes for misery. Long,⁴⁷ however, believes that in time preventive medicine will be taught entirely by the clinical approach, and that when it reaches this ideal a separate department will be unnecessary. This ideal represents an advance in the philosophy of preventive medicine that, when fully realized, will mean that the physician is truly educated to its possibilities.

* * *

The recent advances in preventive medicine have been as diverse as the subject itself. This paper has touched lightly upon a few of them. Perhaps the accomplishments most significant have not been mentioned, for these lie in the invisible realm of thought. Yesterday, on the threshold of bacteriologic science, Sir William Osler said, 'preventive medicine is the medicine of the future,' and today, on the threshold of the atomic era, one can say that without preventive medicine there will be no future.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

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CASE 35261

PRESENTATION OF CASE

A fifty-five-year-old businessman entered the hospital because of abdominal pain and vomiting.

One night six weeks before admission the patient awoke feeling nauseated, and vomited several times. There was no pain. Business and family worries had been plaguing him, and for several months he had felt tense and nervous. After this episode he remained in bed for four days, and then returned to work. Late at night following days on which financial problems had been particularly trying, spells of painless vomiting recurred. Two weeks before admission he left work. The nocturnal vomiting became more frequent and began to be accompanied by severe cramps starting in the back and radiating around to the midline in a viselike manner. He was given pills and put on a bland diet without relief. Two days before admission the frequency of vomiting increased to every two or three hours, no food or fluid was retained. The vomitus consisted of food, fluid and mucus without blood. The bowels had been moving only with laxatives or with enemas. The stool color was normal. During this illness there was a 25-pound weight loss.

During examination the patient was tense and uncomfortable, constantly shifting position in an effort to relax. When the activity reached a peak, he vomited. The speech was rambling, and he had difficulty recalling dates and time. The heart was normal. There was dullness over the left lower lobe posteriorly and in the left axilla, breath sounds and tactile fremitus being reduced in the same areas. The abdomen showed tenderness and spasm throughout the epigastrium. Peristalsis was active. There were no masses.

The temperature was 98.6°F, the pulse 88, and the respirations 20. The blood pressure was 135 systolic, 90 diastolic.

Examination of the blood revealed a hemoglobin of 14.6 gm per 100 cc and a white-cell count of 9600. The urine gave a + test for albumin, and the sediment contained rare casts. The icteric index was 13.

In the hospital the patient was tense and frequently nauseated but appeared to obtain considerable relief from hot baths so that he stopped vomiting and was able to drink water. On the third hospital day the skin and scleras were slightly jaundiced. A surgical consultant found a tender mass in the epigastrium extending to both sides of the midline, but slightly more to the left. The edges of the mass were indefinite, the whole mass was about 15 cm in diameter. Rectal examination was negative. On the same day the gastrointestinal series showed some thickening of the gastric folds, and there was evidence of pressure along the lesser curvature and the posterior wall. The duodenal loop was enlarged (Fig 1), the second portion was displaced to the right and showed evidence of somewhat lobulated compression from the region of the pancreas that also displaced the third portion of the duodenum downward. There were several diverticula in the colon. The spleen was enlarged. There was considerable fluid in the left pleural cavity. Linear areas of atelectasis showed in both lower lobes of the lungs, and the motion of both leaves of the diaphragm was slightly limited. On the following day the icteric index was 25, and the serum amylase was 78 units per 100 cc. Three hundred and fifty cc of opaque, amber fluid, which proved to be sterile, was removed from the left chest. The temperature remained normal.

An operation was performed on the fifth hospital day.

DIFFERENTIAL DIAGNOSIS

DR RICHARD WARREN. This case presents the problem of differential diagnosis of an epigastric mass, which caused considerable vomiting, slight jaundice and fluid in the left chest. I think we can assume at the outset that since most of the symptoms were localized in the epigastrium, the fluid in the left chest was a sympathetic effusion from infradiaphragmatic disease. Furthermore, it seems logical to suppose that this infradiaphragmatic disease was not necessarily of a suppurative nature. The normal white-cell count would not necessarily convince me of this, were it not also true that the pulse and the temperature were normal. Conditions, therefore, that might lead to the more conventional type of subhepatic and left subdiaphragmatic abscess, such as perforated peptic ulcer and phlegmonous gastritis with abscess, I tend to put into the background. This decision is particularly forceful if one considers that the gastrointestinal series showed no evidence of either.

A perforated gall bladder is unlikely for the same reasons, in addition to the fact that the symptom of pain did not make itself evident until well along in the present illness.

There is so much evidence in this case pointing toward the pancreas—namely, the depression of the lesser curvature of the stomach, the displace-

ment laterally of the second portion of the duodenum, the pain in the back, the elevated serum amylase and the slight jaundice — that it is difficult to escape the conclusion that the lesion was in that organ.

The question regarding the nature of the disease then arises. I believe there are two major types to be considered. The first, and least likely, is apoplexy or rupture of some branch of the splenic artery that could cause a large mass in this region and simulate disease of the pancreatic parenchyma itself. Such ruptures, however, are usually catastrophic and run a more rapid course than this. Furthermore, a hemorrhage causing a mass of this size would have caused an anemia, which was not present. I would vote against apoplexy.

The second type of disease in this patient, and the one that I feel to be most likely, is acute pancreatitis with areas of pancreatic necrosis leading to formation of a so-called pseudocyst of the pancreas. Such a cyst very often occupies the whole lesser omental cavity extending to the diaphragm and causing sympathetic pleural effusion above. It generally contains a serous type of fluid with active pancreatic enzymes within it, although these enzymes often erode small blood vessels and cause rather massive bleeding within the cavity of the cyst. If the cyst is seen early it may contain broken down bits of pancreatic tissue and then is generally termed a pancreatic abscess. The jaundice is caused by inflammatory edema of the head of the pancreas — squeezing of the lower end of the common duct rather than encroachment on the common duct by the cyst. I am not prepared to say definitely what the contents of this cyst were but believe they were of such a nature as to put the mass on the borderline between pancreatic abscess and pancreatic cyst. My diagnosis, therefore, is a large inflammatory pseudocyst of the pancreas causing pleural effusion.

DR REGINALD LINGLEY To begin with, I think this would have to be a tumor of the pancreas. The duodenal loop is tremendously enlarged. There is pressure on the lesser curvature of the stomach so frequently associated with pancreatic tumor. The irregular mucosa in the second portion of the duodenum and the presence of what looks like small nodules are very much against a cyst. A cyst of the pancreas is sharply defined and smoothly rounded. Although it can produce a pressure defect on the fundus of the stomach and enlargement of the duodenal loop, the enlargement is smooth and sharply defined whereas this is quite nodular. This is not a usual place for an aortic aneurysm. We usually see it on the left side. This extends to the right and corresponds exactly to the head of the pancreas. In addition to the abdominal findings we have fluid in the chest on the left and areas of atelectasis.

DR CLAUDE E. WELCH This was an interesting problem in differential diagnosis. The rapid appearance of the epigastric mass, with jaundice and left pleural effusion combined with severe prostration, made me believe that we were probably dealing with a subacute pancreatitis and a large pseudocyst of the pancreas. Carcinoma of the pancreas was considered as an alternative possibility.

The patient's rapid decline made it clear that unless some dramatic relief could be obtained rapidly by operation he would die. Accordingly he was explored with little delay. At operation he was



FIGURE 1

found to have a great deal of bloody fluid throughout the abdomen, with small nodules that were grossly typical of fat necrosis. There was a large hard mass involving the entire pancreas and posterior wall of the stomach. Several of the nodules were removed for biopsy, and a jejunostomy was performed.

CLINICAL DIAGNOSIS

Acute pancreatitis

DR WARREN'S DIAGNOSIS

Inflammatory pseudocyst of pancreas

ANATOMICAL DIAGNOSES

Adenocarcinoma of pancreas, with retroperitoneal and splenic extension, and with microscopic metastases to lungs and kidney

Hydrothorax, bilateral

Atelectasis, left lung

Adenoma of islets of Langerhans, microscopic

DR TRACY B MALLORY The biopsy specimen removed by Dr Welch showed a tumor that we thought was epithelial in origin and consistent with primary cancer of the pancreas. The patient went rapidly downhill after operation and died. At post-mortem examination we found the pancreas almost totally replaced by tumor. The same tumor had grown into the hilus of the spleen and occupied two thirds of the spleen. There were metastatic extensions along the retroperitoneal lymph nodes, no metastases in the liver and microscopic metastases to the lung. The sections confirmed the original impression that this was a primary carcinoma of the pancreas. The fact that it had involved the spleen so extensively would suggest that it started near the tail of the pancreas and only secondarily reached the head.

CASE 35262

PRESENTATION OF CASE

A seventy-two-year-old widow was admitted to the hospital because of pain in the right knee.

Thirty to forty years before admission the patient first noted pain, swelling and stiffness of her knees. Multiple tooth extractions and a tonsillectomy and adenoidectomy were done. She was told that she had "tapioca in the knees," and this was aspirated. An infection developed in her left knee following this procedure and drained for a long time. Both knees were ankylosed. Subsequently she had gradual involvement of all joints, with progressive ankylosis and deformity. Twenty-seven years before admission she was treated with a two-month course of radium water, with no relief. Ten years before admission when the right ankle became ankylosed in inversion, the patient received treatments to stretch the ligaments. During this procedure the right tibia and fibula were fractured. The patient became progressively more crippled, with discomfort and stiffness of the joints. There was no real pain until a year before admission, when, while being lifted, she felt her right knee crack. Since then she had constant pain in the right knee, which became swollen. There was no increased heat or redness. An x-ray film showed a pathological fracture with rarefaction of the medial portion of the end of the femur. There were no constitutional symptoms, and in general she felt well.

Six years before admission a uric acid stone was removed from the left kidney.

On physical examination the temperature, pulse and respirations were normal. The blood pressure was 140 systolic, 80 diastolic.

There was limited motion and deformity of all joints. The right knee was swollen and tender, most marked medially. There was no motion of either knee.

The specific gravity of the urine was 1.020, and there was a + test for albumin. The hemoglobin was 13.2 gm and the white-cell count was 8000, with a normal differential. The sedimentation rate was 1.33 mm per minute, and the hematocrit was 40 per cent. The blood serum calcium was 9.3 mg, and the phosphorus 4.2 mg per 100 cc, and the phosphatase was 3.4 units.

An x-ray examination of the right knee showed a markedly narrowed joint, and the adjacent bones were extensively osteoporotic, consistent with old rheumatoid arthritis. Occupying the medial distal extremity of the femur was a large area of bone rarefaction measuring 10 cm in length by 8 cm in width (Fig 1). There was a thin cortical shell medially and posteriorly, while in places there appeared to be loss of continuity of the cortex without, however, frank extension of the mass into the adjacent soft tissues. The lesion had definitely grown in size in comparison with the films taken elsewhere, three months before admission. The femoral shaft above the lesion appeared dense, and its trabeculae somewhat wider than in the left knee, which showed extensive changes of old rheumatoid arthritis.

On the eighth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR THOMAS ANGLEM* We might start by looking at the x-ray films.

DR STANLEY M WYMAN This is the original film taken elsewhere, and here is a film taken in comparable projection three months later. The area of bone rarefaction is well demonstrated in the distal femur occupying the femoral condyles. There is an unusual accumulation of amorphous, very dense calcification seen in the lateral aspect of the lesion, with a few small less definite areas of calcification in this region. This is present on both films, and

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is seen on other projections to lie definitely in the lesion. The increase in size in the mass is quite apparent compared to the films in similar projection, and one can make out tiny slivers of what I take to be cortical bone remaining, with, in a few places, loss of continuity of the bone. The shaft of the right femur is denser than the left, but the findings are not typical of Paget's disease. Changes, which are quite typical of old, long-standing rheumatoid arthritis, are seen in both knee joints, and osteoporosis is also well demonstrated.

DR. ANGLE: There are many significant points in this history. The patient had pain in the knee for one year. It seems clear that she had an unmistakable rheumatoid arthritis, which however I do not believe had any bearing on the real issue in this case. Twenty-seven years before admission she had a course of treatment with radium water. This may be a red herring, but on the other hand it may have played a definite part in the etiology of this lesion. Ten years before entry she sustained a fracture of the right tibia and fibula in the course of manipulation of the foot for inversion, which suggests that the bone was unusually friable and this may perhaps be classed as a pathological fracture. In the course of her present illness she sustained another pathological fracture of the right knee while being lifted. Six years before admission she is reported as having had a uric acid stone of the kidney. Another point that seems of some significance is that she was said to have felt well otherwise. Her only complaint was with reference to the pain in the knee.

On examination the knee showed swelling and tenderness. Her laboratory findings showed nothing of particular significance. The urine gave a + test for albumin. The blood was virtually within normal limits, with a normal calcium, phosphorus and phosphatase, and the sedimentation rate was within normal limits.

The diagnosis, I believe, will rest chiefly on the interpretation of the x-ray films. I think the first thing one has to decide about this lesion is whether it was a benign bone cyst of some kind or a tumor — if a tumor, whether it was benign or malignant, primary in bone or metastatic.

Regarding bone cyst, I am certain that this was not a solitary bone cyst, which usually occurs in the shaft of long bones and is extremely uncommon at this age. The cysts occur almost entirely in childhood or adolescence and are very rare after

twenty-one years of age. I believe that we can dismiss bone cyst.

The possibility of cystic change in the bone secondary to parathyroid adenoma is suggested, at least superficially, by the history in this case. The x-ray films are reported as showing some osteoporosis



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renal calculus was a uric acid and not a calcium stone. I think that we can dismiss benign cystic disease of bone and consider the tumors.

Was this a benign tumor? The only benign tumor that is suggested to me is benign giant-cell tumor. There are features that suggest it rather markedly. The position of the lesion — at least the involvement of the epiphysis — is characteristic of benign giant-cell tumor, and the general contour of the lesion is similar to what one sees in benign giant-cell tumor in this area. On the other hand the degree of extension up the shaft of the bone is unusual, and the areas of density described are not commonly seen in benign giant-cell tumor. The so-called aggressive type of giant-cell tumor, which is undergoing malignant change, must be considered. I believe that this was a malignant tumor, and whether or not it was primary or secondary must still be considered.

Another primary tumor that one has to consider in patients of this age is solitary myeloma. It occurs frequently in old people, although it is not a common disease. Opposed to this diagnosis we have the fact that the patient felt well otherwise, which is not usually the case with myeloma. The patient with myeloma usually has some degree of general malaise, weakness and a greater degree of anemia than this patient showed. There is no report of Bence-Jones protein in the urine, and while its absence is not particularly significant, it would be of significance if present. The serum protein is not reported, it is usually elevated with myeloma. The sedimentation rate is also usually elevated. The x-ray appearance of the lesion does not suggest myeloma.

Reticulum-cell sarcoma must be considered although it is not common at this advanced age. It occurs generally, however, in the shaft of the bone, and the osteolytic lesions produced by this disease do not resemble the x-ray picture that we see in this case. I do not believe that we are dealing with reticulum-cell sarcoma.

Of the primary tumors of bone the diagnosis that I am most strongly attracted to as an explanation of this patient's difficulty is osteolytic osteogenic sarcoma. There may or may not have been a relation between this patient's history of ingestion of radium water twenty-seven years previously, and the lesion in question. During the past twenty-five to thirty years there have been a

quack remedies on the market purporting to contain radium. Many did not, but on the other hand there were some that actually did contain radioactive material. If the so-called radium water actually contained radioactive substance it may have been responsible for this lesion. One point that is a bit further suggestive of this possibility is the reported appearance of osteitis in the shaft of the femur above this lesion. Osteogenic sarcoma when it occurs as the result of radioactive material occurs on the basis of pre-existing osteitis, which is caused by the radioactive material in the bone. We have some evidence here of a pre-existing osteitis that may have been of significance in the development of this degenerative lesion.

One has to consider metastatic lesions in this case. And, of course, the strongest point against metastasis is the complete absence of anything in the history or physical examination suggestive of a primary lesion elsewhere. Of the types of malignant tumors of soft tissue or other parts of the body capable of producing osteolytic bone lesions, the most common are breast, thyroid, kidney and adrenal gland, and of these the breast is by all odds the commonest. On the other hand it is very unusual for breast cancer to produce metastases without the breast lesion itself being easily discoverable clinically. It is not mentioned in this history. Carcinoma of the thyroid gland, adrenal gland and kidney may produce metastatic lesions of bone, and they may make their appearance some time before the primary disease is discovered. These possibilities have to be considered, but they do not as a general rule occur in the end of long bones.

On a purely statistical basis, a lesion such as this, even a solitary lesion, occurring at this age is several times more likely to be metastatic than a primary tumor of bone. On the other hand the definite history of ingestion of radium water and the appearance of the lesion on x-ray examination tempt me to make a diagnosis of osteolytic osteogenic sarcoma secondary to radiation osteitis from the ingestion of so-called radium water.

DR. WYMAN: There is one point to add to Dr. Anglem's excellent discussion. We did not have the history of the ingestion of radium water at the time the films were interpreted, and we tended to a diagnosis of osteogenic sarcoma based on possible Paget's disease. However, this is by no means the picture we usually see in Paget's disease, and I

her favor Dr Anglem's diagnosis, knowing about the radium now

CLINICAL DIAGNOSIS

Osteogenic sarcoma

DR ANGLEM'S DIAGNOSIS

Osteolytic osteogenic sarcoma secondary to ingestion of "radium water"

ANATOMICAL DIAGNOSIS

Fibrosarcoma of femur, invading knee joint, possibly related to ingestion of "radium water"

PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY About a dozen years ago we had a patient in this hospital who was likewise an arthritic and had taken so-called radium water for treatment. She kept it up for a long period, several years, and samples were tested and proved actually to contain radioactive substances. In the case under discussion we have not that positive evidence. The other patient developed a tumor of the knee in exactly the same location as this patient, and the lesion turned out on pathological examination to be a fibrosarcoma, which rapidly metastasized and caused her death.

It is a rather striking coincidence that in the case under discussion the tumor was also in the knee region, involving both the femur and the knee joint, and was also a fibrosarcoma rather than an osteogenic sarcoma. We were not able to demonstrate any radioactivity of tumor or bones. Examination with a Geiger counter was negative, whereas in the preceding case it was definitely positive. But I have a rather strong suspicion that the radioactive material may have had something to do with the development of the tumor but cannot prove it.

DR WYMAN What were the changes found in the bone proximal to the lesion?

DR MALLORY Not very striking — mild osteoporosis was all we found. In the earlier case the changes were much more extensive, and there was a marked hematopoietic reaction in the bone marrow of the femur, it almost suggested the picture of pernicious anemia.

The lesion occupies the lower end of the shaft of the femur. It extends up beyond what was the epiphyseal line into the diaphysis. The knee joint is completely fused by the old arthritic and septic process. With the specimen in one's hand one can see that the tumor has extended across the slight remnants of the joint space and involved the posterior surface of the patella.

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LICENSURE OF FOREIGN GRADUATES

THE Council on Medical Education and Hospitals of the American Medical Association, taking cognizance of the number of foreign physicians who are entering this country with the hope of establishing themselves here, has sponsored an unofficial committee on foreign medical credentials. The membership of this committee is made up of representatives of a number of organizations, including several state licensing boards. Its function is to investigate the entire matter of the licensing of foreign medical graduates and to make recommendations for the solution of the problems involved.

The difficulties that have arisen concerning these physicians, many of them inadequately trained as a result of thirty years of unsettled conditions abroad, have been recognized for some time, and the manner in which they have been met has already been discussed in these columns.*

The migration to the United States of foreign schools began about 1926, and of this and conditions brought about War II, many states have raised their requirements for licensure. The New York Board of Medicine, for instance, no longer admits to the state licensing examination graduates of European medical schools who matriculated since January 1, 1914, with the possible exception of graduates of the universities of Cambridge, of London, of Dublin, and of Ireland. This drastic step has been taken for due cause, in the last twenty years 66 per cent of the foreign physicians taking the examination have failed to pass. In Massachusetts no graduate of any foreign medical school who matriculated later than January 1, 1941, have been permitted to register, except those from Canada.

These matters require serious study in order that foreign schools may as soon as possible be evaluated as are those in the United States and Canada. Reasonable justice in licensure cannot be achieved until the quality of the training of applicants can be appraised.

ANNALS OF WORLD HEALTH

THREE years ago the first steps were taken to organize an international health conference. The conference prepared a constitution for the proposed World Health Organization, which became an official specialized agency of the United Nations in April 1948, after 26 member nations had signified their acceptance of the constitution. By January of 1950, 58 nations had become members of WHO.

WHO now publishes in English, French, Spanish, Russian and Chinese each month the *Chronique*, which contains general information concerning the trend of its work and summaries of its most technical publications, the *Bulletin*, which presents signed articles on subjects under consideration by the organization such as the control, prophylaxis and treatment of malaria, tuberculosis, venereal and epidemic diseases, a weekly epidemiologic record, epidemiologic and vital-statistics reports, and fifteen volumes of official records. These publications are obtainable at moderate cost from the sales section of WHO, Palais des Nations, Geneva.

*Editorial "Of thee I sing," *New Eng J Med* 239:152, 1948.

expressed aim of the World Health Organization—the improvement of the physical, mental and health of all peoples. Such improvement is badly needed. It was thought that progress is usually being achieved in this direction before it is a generation of cataclysmic disintegration. No one is skeptical of the capacity of the human mind for any sort of co-operative effort. WHO offers the few remaining opportunities to demonstrate that such skepticism is not justified. If science, the humanities and religion can get out of politics, there is still hope. May this noble organization be able to point to continued growth and achievement three years hence!

DR. BERRY AT HARVARD

NEW dean for Harvard Medical School has been selected and will take office on July 1, 1949. Dr. C. S. Burwell, who has held the administrative post for nearly thirteen years and who announced earlier in the academic year his intention of returning to teaching and research, is to be succeeded by Dr. George Packer Berry, at present professor of bacteriology and associate dean of the School of Medicine and Dentistry at the University of Rochester.

In addition to his deanship Dr. Berry, whose previous investigative work has been in the fields of immunology and virology, will hold an appointment as professor of bacteriology.

A native of Troy, New York, Dr. Berry graduated from Princeton University in 1921 and from the Johns Hopkins University School of Medicine in 1925. After resident services in the Connecticut State Hospital for the Insane, in Bellevue Hospital in New York and in the Johns Hopkins Hospital, he became an assistant and later instructor in medicine in Johns Hopkins University School of Medicine. From 1929 to 1932 he was assistant resident physician in the Hospital of the Rockefeller Institute for Medical Research and an associate of the Institute. He became professor and head of the Department of Bacteriology and associate professor of medicine at Rochester in 1932, and in 1947 became associate dean. In 1946 Dr. Berry, as an officer

of the Naval Reserve on active duty, took part in the atomic-bomb tests at Bikini Atoll.

Dr. Berry is a diplomate of the American Board of Internal Medicine and a fellow of the American Association for the Advancement of Science, the American Public Health Association and the American



GEORGE P. BERRY, M.D.

can Medical Association. A former president of the American Association of Immunologists, he has also served as vice-president of the Association of American Medical Colleges.

The *Journal*, in welcoming Dr. Berry to New England, at the same time congratulates Harvard on his acquisition, wishing them both a mutually profitable and extended relationship.

A GOOD INSECTICIDE, NOT A POISON

A STATEMENT was recently issued by the Department of Agriculture and the Federal Security Agency calling attention to the proved value of DDT as an insecticide. Some public alarm has been caused by misleading comments concerning possible haz-

ards connected with the use of this chemical It is pointed out that DDT has contributed materially to the welfare of the world, and should not be brought into disrepute through overemphasis of the well recognized fact that it has toxic properties, especially if improperly used The ingestion of a tube of toothpaste, or a cake of soap or a bottle of cleaning fluid might be injurious or fatal, and yet they are harmless and useful substances if properly employed

The fact that DDT, like other insecticides, is a poison, has been given full consideration in the formulation of recommendations for its use "There is no evidence that the use of DDT in accordance with the recommendations of the various Federal agencies has ever caused human sickness due to the DDT itself despite the fact that thousands of tons have been used annually for the past four or five years, in the home and for crop and animal protection" As a precautionary measure modifications of recommendations have recently been made by the Department of Agriculture for the use of DDT on dairy cattle There is, however, no justification for any public alarm about the safety of the milk supply from the standpoint of possible DDT contamination This has been agreed upon by the Department of Agriculture, the Army and the Navy, the Pan-American Sanitary Bureau and the Federal Security Agency

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

COFFIN — Susan M Coffin, M.D., of Boston, died on June 1 She was in her sixty-ninth year
Dr Coffin received her degree from Boston University School of Medicine in 1910
A nephew survives

CONDRIK — James F Condrick, M.D., of Quincy, died on May 27 He was in his sixty-fourth year
Dr Condrick received his degree from Tufts College Medical School in 1919
His widow survives

GIDDINGS — Harold G Giddings, M.D., of Newton, died on May 28 He was in his seventieth year
Dr Giddings received his degree from Harvard Medical School in 1907 He was a member of the staff of the Newton-Wellesley Hospital and of the Board of Consultation of the Massachusetts General Hospital and was formerly chief of surgery of the Whidden Memorial Hospital in Everett He was a former president of the Middlesex South District Medical Society and chairman of the Committee on Arrangements of the Massachusetts Medical Society, for many years he had been a counselor of the Society He was also a fellow of the American College of Surgeons
His widow, two sons and a sister survive

McCORMICK — William A McCormick, M.D., of New Bedford, died on February 21 He was in his fifty-eight year

Dr McCormick received his degree from Tufts College Medical School in 1914

His widow, a daughter, a brother and three sisters survive

MULHERN — Joseph P Mulhern, M.D., of Worcester died on March 6 He was in his fifty-eighth year

Dr Mulhern received his degree from Tufts College Medical School in 1918 He was a visiting surgeon, orthopedic service, St Vincent Hospital, member of the courtesy staff in orthopedics, Hahnemann Hospital, and consulting surgeon in orthopedics and president of the board of trustees Worcester City Hospital He was a fellow of the American College of Surgeons and American Medical Association

His widow, six daughters and two sons survive

NEW HAMPSHIRE MEDICAL SOCIETY

DEATH

ABBOTT — Edson M Abbott, M.D., of Rochester, died on May 14 He was in his eighty-first year

Dr Abbott received his degree from University of Vermont College of Medicine in 1898

His widow survives

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The July schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows

CLINIC	DATE	CLINIC CONSULTANT
Haverhill	July 6	William T Green
Salem	July 11	Paul W Hugenberger
Gardner	July 12	Carter R Rowe
Springfield	July 12	Garry deN Hough, Jr
Brockton	July 14	George W Van Gorder
Worcester	July 15	John W O'Meara
Pittsfield	July 20	Frank A Slowick
Fall River	July 20	David S Grice
Yanniss	July 28	Paul L Norton

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments Patients are seen by appointment only

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR APRIL, 1949

DISEASE	RÉSUMÉ		
	APRIL 1949	APRIL 1948	SEVEN YEAR MEDIAN
Chancroid	5	0	2*
Chicken pox	2485	1973	1973
Diphtheria	42	18	18
Dog bite	1281	1107	1073
Dysentery bacillary	2	12	7
German measles	1011	130	398
Gonorrhea	249	254	332
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	0	1	2*
Malaria	1	3	4
Measles	3921	5950	5512
Meningitis meningococcal	2	3	16
Meningitis Pfeiffer-bacillus	8	2	3
Meningitis pneumococcal	2	0	0
Meningitis staphylococcal	0	0	1
Meningitis streptococcal	1	2	4
Meningitis undetermined	1346	2614	1483
Mumps	1	0	1
Poliomyelitis	2	16	6
Salmonellosis	652	812	1422
Scarlet fever	198	256	342
Syphilis	282	242	232
Tuberculosis pulmonary	16	6	14
Tuberculosis other forms	3	3	3
Typhoid fever	2	3	3
Undulant fever	281	183	499
Whooping cough			

*Five year median

COMMENT

Diseases whose incidence was above the seven-year median were chicken pox, diphtheria, German measles and typhoid fever

Diseases whose incidence was below the seven-year median were bacillary dysentery, measles, mumps, salmonellosis, scarlet fever and whooping cough

Diphtheria was at the highest level for the month of April since 1934

The seasonal peak for measles was reached in March this year, and that for scarlet fever in February

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Arlington, 1, Ayer, 1, Billerica, 1, Boston, 30, Cambridge, 4, Malden, 2, Quincy, 2, Somerville, 1, total, 42

Dysentery, amebic, was reported from Brookline, 1, total, 1

Dysentery, bacillary, was reported from Brockton, 1, Wrentham, 1, total, 2

Encephalitis, infectious, was reported from Marshfield, 1, Needham, 1, Watertown, 1, Worcester, 1, total, 4

Infectious hepatitis was reported from Newton, 1, Norwood, 1, Wrentham, 6, total, 8

Lymphocytic choriomeningitis was reported from Fitchburg, 1, Framingham, 1, Somerville, 1, total, 3

Malaria was reported from Lynn, 1, total, 1

Meningitis, meningococcal, was reported from Newton, 1, Worcester, 1, total, 2

Meningitis, Pfeiffer-bacillus, was reported from Brockton, 1, Gardner, 1, Haverhill, 1, Hull, 1, Milton, 1, Salem, 1, Westfield, 1, West Springfield, 1, total, 8

Meningitis, pneumococcal, was reported from Fall River, 1, Worcester, 1, total, 2

Meningitis, undetermined, was reported from Braintree, 1, Fall River, 1, Taunton, 1, Wakefield, 1, total, 4

Poliovirus was reported from Springfield, 1, total, 1

Salmonellosis was reported from Greenfield, 1, Newton, 1, total, 2

Septic sore throat was reported from Boston, 6, Cambridge, 1, Lynn, 2, Templeton, 1, total, 10

Tetanus was reported from Milford, 1, total, 1

Trichinosis was reported from Cambridge, 1, total, 1

Typhoid fever was reported from Boston, 1, Cambridge, 1, Fairhaven, 1, Lakeville, 1, Randolph, 1, total, 5

Undulant fever was reported from Dartmouth, 1, Ware, 1, total, 2

DISCONTINUANCE OF PAPANICOLAOU SMEAR SERVICE

Because of the large number of smears, and as a result of curtailment of federal funds allocated to the Department of Public Health, it has become necessary for the Massachusetts State Tumor Diagnosis Service to discontinue its service of Papanicolaou smear diagnosis to the cancer clinics of the Commonwealth for the time being

CORRESPONDENCE

DR FROTHINGHAM IN REBUTTAL

To the Editor I appreciate your giving me an opportunity to reply to Dr Rawls's letter published a week ago in the *Journal*. May I also take this opportunity to commend your attitude of offering all sides an opportunity to present their viewpoint on this controversial subject of the development of a national health program

If one will read the inaugural address of Dr Rawls mentioned in his letter and my letter in the February 17 issue of the *Journal* I believe it will be evident that Dr Rawls's letter adds nothing to the clarification of my claim that in his inaugural address there were misstatements of fact and misleading innuendoes. Therefore it seems to me that no useful purpose will be served in discussing the various statements in his letter

I should like, however, to say that the Committee for the Nation's Health has never tried to hide the fact that it endeavors to influence legislation in a proper manner, and in accordance with law has always registered as lobbyists members of the group who are paid for this service. In addition to this activity the Committee devotes much more of its time in endeavoring to unite throughout the country the millions of citizens who are interested in the development of a national health program to be financed in part by compulsory health insurance and in educating all the people in the value of such a program

CHANNING FROTHINGHAM, M.D.

Chairman, Committee for the Nation's Health
101 Bay State Road
Boston 15, Mass

DRAMAMINE IN MENIÈRE'S DISEASE

To the Editor For the past thirteen years, I have suffered from Ménière's disease, with only temporary relief from any form of treatment that has been tried

In March, 1949, having read about the effect of dramamine on motion sickness, as used by Dr Leslie N. Gay and Dr P. E. Carlner at the Johns Hopkins Hospital in Baltimore, I communicated with a representative of G. D. Searle and Company, and Dr Lee D. van Antwerp, about the effect of dramamine on Ménière's disease. I received the following reply from Dr van Antwerp:

At the present time there is no information available concerning the usefulness of dramamine in Ménière's disease, but we readily recognize a causal relation between the pathology of that condition and the presumed disturbed physiology of motion sickness. It is my understanding that Dr Leslie N. Gay, of Johns Hopkins, is currently conducting a study of the usefulness of dramamine in Ménière's disease, although his information is not yet complete

I then communicated with Dr Carlner and asked him if they had had any experience with the use of dramamine in Ménière's disease. Dr Carlner replied that they had 30 people on dramamine in their investigative work, and I asked to be added to the list. I have been on dramamine since March 15, 1949, with a dramatic and immediate cessation of all vertigo and a 75 per cent improvement in tinnitus and some improvement in hearing in my left ear

In April, 1949, I asked Dr Henry L. Haines, of New London, Connecticut, to try dramamine on patients who had Ménière's disease. He now informs me that he has put 3 patients on the drug with immediate and dramatic improvement

It is hoped that further experience with the use of dramamine in the treatment of Ménière's disease may be obtained so that its benefits can be accurately determined

WILLIAM V. WENER, M.D.

Norwich, Connecticut

BOOK REVIEWS

Peripheral Vascular Diseases: Diagnosis and treatment. By David W. Kramer, M.D. With a foreword by Edward L. Bortz, M.D. 8^{vo}, cloth, 620 pp., with 157 illustrations. Philadelphia: F. A. Davis Company, 1948. \$8.00

This vascular-conscious period welcomes a treatise based on practical experience and aimed at correlating the accelerated contributions to this ever-expanding field. With this view in mind, Dr Kramer has succeeded in presenting a readable, lucid, orderly discourse, supplemented with excellent illustrations and tabular differential diagnoses, on peripheral vascular diseases that should constitute a reliable *cadre mecum* for the student, general practitioner and internist.

The subject is treated comprehensively in five parts, as follows: symptoms, signs and tests, occlusive arterial disorders, vasomotor disturbances, gangrene and ulcers, and veins, anticoagulants, antibiotics and lymphedema. In the first section on history, symptoms, signs and tests, it is pleasing to see the term "claudication" unmasked and called

by its synonymous term "cramps" — whether of the intermittent or rest type. In the reviewer's teaching and clinical experience, the term "intermittent claudication" always seemed to connote to the uninitiated a symptom pathognomonic only of thromboangitis obliterans. In the same section the author misses an opportunity, however, to stress the value of inquiring into the history of ingestion of various drugs causing peripheral vascular disease, notably ergot. He does, it is true, devote a later discussion on ergotism under the heading of gangrene and ulcers. In neither the former section under color, as a sign, nor in the latter, does the author refer to the frequently observed, tell-tale, coxcomb color, which characterizes this type of lividity. There is an excellent, illustrated discussion on focal gangrene in diabetes in this section. The chapter on tests is a specific and well illustrated presentation, with a final evaluation. The new tropidore method for reflex vasodilatation carries no reference, it might be the author's own technic, of course. In actual performance, it appears that the author favors the histamine test for capillary appraisal, the sphygmomanograph or recording oscilometer for arterial trunk evaluation, and dermathermic, skin-temperature determinations, before and during general anesthesia by gas, gas ether or cyclopropane, rather than paravertebral block, for vasomotor response. The skin-temperature charts, though simple and adequate, might be labeled more clearly or revised for the purpose of more precise exposition.

In the second section, on occlusive vascular disorders, there is an excellent discussion of acute arteritis, periarteritis nodosa and endarteritis obliterans, as well as the more common conditions. Apropos of the statement under thromboangitis obliterans that failure of increase in skin temperature after vasomotor tests constitutes a contraindication to ganglionectomy, the reviewer's experience to the contrary does not permit him to subscribe to this only partly correct view. Likewise, issue might be taken with Dr Kramer's statements that ganglionectomy is attended by an objectionable "mortality rate" (not specified) and that it is a "formidable" procedure. Regarding embolic occlusion, no reference is made to the limb-saving procedure of radical decompressing fascial incisions in popliteal-artery embolism or acute thrombosis.

In the section on vasospasm the author presents a clear picture of the various and obscure conditions mediated by neuroendocrine dysfunction. This clarification of Raynaud's disease, scleroderma, scalenus anticus syndrome, pneumatic hammer disease, erythromelalgia and so forth is a valuable contribution to understanding of the etiology and clinical characteristics of this perplexing group of conditions. Under Raynaud's disease the author does not stress the currently accepted doctrine of preganglionic section. In the treatment of the acute phase of traumatic arteriospasm, paravertebral ganglionic block, repeated if necessary, is not mentioned.

A good résumé of the entire field of peripheral vascular disease from the obverse side is afforded in the fourth section on gangrene and chronic leg ulcers with, however, several surgical shortcomings, such as failure to mention femoral-vein ligation, lumbar ganglionectomy and the Linton operation in the treatment of chronic varicose and post-phlebotic ulcers.

The last section is devoted to veins, antibiotics and lymphedema with, again, characteristic excellent clinical descriptions. The ubiquitous problem of varicose veins is discussed fully, and in its development, the discussion contains a desirable and complete review of the various tests employed in the study of this condition. From the surgical point of view there is room for disagreement with the author's preference for high saphenous ligation and retrograde sclerosing injection in the light of the modern trend toward stripping, total or segmental, or multiple ligation, or both.

To the reviewer Dr Kramer's book is obviously an internist's treatise, lacking in the highly important details of surgical treatment. In the light of this criticism it cannot be accepted that the author fulfilled his aim, as stated in the preface, of "the value of explicitness" in the treatment of these disorders. The author might have warned the reader of his legitimate limitation of discussion of surgical techniques to general terms. This treatise does, however, "lead the reader through the basic subjects into diagnosis and treatment" with clarity, ease of style and a wealth of bibliographic information.

Premature Infants. A manual for physicians. By Ethel Dunham, M.D. 8°, paper, 401 pp., with 31 illustrations and frontispiece. Washington, D.C.: United States Government Printing Office, 1948. \$1.25. Children's Bureau Publication No. 325, 1948.

It may be said that this so-called manual constitutes an up-to-date treatise on prematurity and the general care of the premature infant. The subject is important, and it is estimated that 5 per cent of all births in the United States fall into this class, and that the single greatest cause of infant mortality in the first month of life is premature birth, which accounts for half of all infant deaths in this period. The text is divided into two main parts: "General Considerations," analyzing the incidence, causes, and prevention of immaturity, and the growth and development of premature infants, and "Clinical Considerations," dealing with physical problems and clinical care, including the neonatal period, resuscitation, incubator care, nutritive congenital malformations and birth injuries, infectious abnormal blood conditions, metabolic and nutritional disturbances and other conditions. Dr Dunham is well qualified to write this comprehensive guide. She received her degree from Johns Hopkins University School of Medicine and taught in the Pediatric Department of the Yale University School of Medicine before joining the Children's Bureau in 1927. She is a member of the American Pediatric Society and a fellow of the American Academy of Pediatrics. The material is well organized, and the text well written. An extensive bibliography is appended to each part, and there is a good index. The type and printing are excellent. The book is worth a number of times its low price and should be in all medical libraries and in the collections of all obstetricians and pediatricians.

Report of the Sanitary Commission of Massachusetts 1850. By Lemuel Shattuck and others. With a foreword by Charles Edward Winslow. 8°, cloth, 321 pp. Cambridge: Harvard University Press, 1948. \$4.50.

This reprint of a classic on public health is only partial for it does not contain the appendix of 218 pages and the index. The original report comprised 544 pages and was issued in a heavy, paper cover. This appendix is important since it contains many of the factual data upon which the report of the Commission was written. The Commission consisted of Lemuel Shattuck, Nathaniel P. Banks, Jr., and Jehie Abbott. Although the report is attributed to the Commission, the actual author was Lemuel Shattuck, of Boston. The partial reprint is preceded by a foreword by C.-E. A. Winslow, a noted expert on the subject, in which he states:

Surely this is an outstanding document for the year 1850 and it has its message for us in 1948. Johann Peter Frank, Chadwick, Simon, Sedgwick, Chapin, have written classics in the science of public health, but I know of no single document in the history of that science quite so remarkable in its clarity and completeness and its vision of the future.

The original report was a state document, and two thousand copies were printed — a large number for the period. Despite this comparatively large number of copies the report is very rare and commands a high price. The reprint is well published and even in its abbreviated form should be in all medical libraries and public-health collections.

Economic Man. In relation to his natural environment. By C. Reinold Noyes. In two volumes. 8°, cloth. Vol. I, 692 pp.; Vol. II, 751 pp. New York: Columbia University Press, 1948. \$15.00 for the set.

This treatise is an important medical reference work. The first six chapters, and their appendixes, of nearly five hundred pages, constitute a mass of new material in the biologic sciences, including physiology and especially neurophysiology, classified under the heading of "wants," present and future. In formulating his synthesis Mr. Noyes has consulted a great number of scattered research articles and reports. Likewise, the most recent research on the brain has been utilized. The work has been in progress for seventeen years. Mr. Noyes, although an economist, has an excellent background for the biologic aspects of his subject. He is a graduate of Yale University, and pursued

special studies at Johns Hopkins University in the Department of Psychology and in the Medical School. Additional extensive research was done in the libraries of the New York Academy of Medicine, Columbia University and Dartmouth College. A bibliography of 450 titles is appended to the text. There is a good index. The treatise should be in all biologic libraries and in the reference collections of medical school and regional medical libraries.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return or the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Thyroid and its Diseases. By J. H. Means, M.D., Jackson Professor of Clinical Medicine, Harvard Medical School, and chief of the medical services, Massachusetts General Hospital. With chapters on *Pathology*, and on *Tumors of the Thyroid*, by R. W. Rawson, M.D., assistant professor of medicine, Harvard Medical School, and associate physician, Massachusetts General Hospital, and on *Surgery of the Thyroid*, by Oliver Cope, M.D., assistant professor of surgery, Harvard Medical School, and visiting surgeon, Massachusetts General Hospital. 8°, cloth, 371 pp., with illustrations. Second edition. Philadelphia: J. B. Lippincott Company, 1948. \$12.00.

This standard treatise has been thoroughly revised and brought up to date since the publication of the first edition in 1937. It reflects the work carried on in the Thyroid Clinic of the Massachusetts General Hospital. Special chapters on surgery of the thyroid gland by Oliver Cope, M.D., and on pathology and on tumors by R. W. Rawson, M.D., have been added. Lists of references are appended to the various chapters, and there is a good index. The volume is a good example of excellent publishing. It is essential for all medical libraries and to all persons interested in the thyroid gland.

The Hygiene of the Breasts. By Clifford F. Dowkontt, M.D. 12°, cloth, 222 pp., with illustrations. New York: Emerson Books, Incorporated, 1948. \$2.50.

This popular manual is written by a surgeon who specializes in plastic surgery of the breasts. It is hoped that it will encourage women to take better care of their breasts. There is a special chapter on corsets. The text is concluded with a glossary of terms and an index.

Manual of Urology. By R. M. LeComte, M.D. Fourth edition. 8°, cloth, 311 pp., with 58 illustrations. Baltimore: Williams and Wilkins Company, 1948. \$4.00.

This manual was first published in 1933. Four years have elapsed since the printing of the third edition. The text has been revised and brought up to date, and the use of penicillin and streptomycin has been included. The volume is intended for the student of urology. The material is well arranged, and there is a good bibliography and an index of subjects. The book is well published.

Neurosurgical Pathology. By I. Mark Scheinker, M.D., assistant professor of neuropathology and assistant professor of medicine (neurology), University of Cincinnati College of Medicine and neuropathologist and attending neurologist, Cincinnati General Hospital. 8°, cloth, 370 pp., with 238 illustrations. Springfield, Illinois: Charles C. Thomas, 1948. \$3.75.

This book is well published. The price is reasonable for this type of publication. The volume should be in the reference collection of all medical libraries and available to all neurosurgeons.

Bronchiogenic Carcinoma and Adenoma. With a chapter on mediastinal tumors. By B. M. Fried, M.D., associate attending physician, Montefiore Hospital for Chronic Diseases,

New York. 8°, cloth, 306 pp., with 118 illustrations. Baltimore: Williams and Wilkins Company, 1948. \$6.00.

In this monograph Dr. Fried discusses the anatomic and physiologic aspects, clinical manifestations, laboratory diagnosis and treatment of bronchiogenic carcinoma and adenoma, and mediastinal tumors. The work is based on a large clinical experience and the study of post-mortem material. Lists of selected references are appended to the different chapters. A good index concludes the text. The volume should be in all medical libraries and should prove of value to all physicians interested in the subject.

Methods in Medical Research. Volume I. Van R. Potter, editor-in-chief. 8°, cloth, 372 pp., with illustrations. Chicago: Year Book Publishers, Incorporated, 1948. \$8.00.

This volume forms the first of a projected series and is the joint work of forty-nine contributors. The text is divided into four sections: assay of antibiotics, circulation and blood-flow measurement, selected methods in gastroenterologic research, and cellular respiration. The various articles present the latest methods, techniques and apparatus pertaining to the special subjects under discussion. Lists of selected references are appended to the more important articles. The work is well published. It is an essential reference book for all medical libraries and clinical laboratories.

Deafness, Tinnitus, and Vertigo. By Samuel J. Kopetzky, M.D., director of the department and professor of otolaryngology, New York Polyclinic Medical School and Hospital. 8°, cloth, 314 pp., with 30 illustrations and 10 tables. New York: Thomas Nelson and Sons, 1948. \$7.50.

This monograph covers the whole field of deafness and allied conditions from anatomy to therapy. The tenth chapter discusses the pathological findings and criteria indicating rationally applied therapy in one hundred pages. Pertinent references are appended to the various divisions of the text. The volume is well published and should be in all medical reference collections and in the libraries of specialists on the subject.

Education for Professional Responsibility. A report of the proceedings of the inter-professions conference on education for professional responsibility held at Buck Hill Falls, Pennsylvania, April 12, 13, and 14, 1948. 8°, cloth, 207 pp. Pittsburgh: Carnegie Press, 1948. \$3.00.

This volume reports a conference participated in by eighteen leaders in the fields of education in divinity, medicine, law, engineering and business. The subject matter is divided into three parts on professional education: the objectives, content and method, and social and humanistic aspects. Medicine was represented on the panel by William W. Beckman, of Harvard, George P. Berr, of the University of Rochester, and Aura E. Severinghaus, of Columbia. A short bibliography concludes the text. The lack of an index detracts from the reference value of the book. The volume is well published and should prove valuable to persons interested in the subject.

Hemolysis and Related Phenomena. By Eric Ponder, The Nassau Hospital, Mineola, New York. 8°, cloth, 398 pp., with 69 illustrations. New York: Grune and Stratton, 1948. \$10.00.

This monograph constitutes a second edition of the author's *The Mammalian Red Cell and the Properties of Hemolytic Systems*, first published in 1934. The text has been amplified and is concluded with a bibliography and indexes of authors and subjects. The publishing is excellent. It is noted with pleasure that a light, soft, nonglare paper has been used for the volume, which should be found in all medical reference collections and should prove useful to specialists in its field.

A Brief History of The South Carolina Medical Association. To which are added short historical sketches of various medical institutions and societies of South Carolina. 8°, cloth, 197 pp., with illustrations and frontispiece. Charleston: South Carolina Medical Association, 1948.

This brief history of the state society also includes the county societies, miscellaneous societies, special societies

and state institutions. The society was founded in 1848, and this volume is issued in commemoration of its centenary. In actuality it comprises a short history of medicine in South Carolina for the past hundred years. There is a special chapter on the ether controversy in which it is claimed that ether was first used for the purpose of producing insensibility by Dr. P. A. Wilhite, of Anderson, South Carolina, in 1841. The text is the joint work of twenty-five authors supervised by a special committee of the Society. A good index concludes the volume. The publishing is excellent.

Hungerkrankheit, Hungerödem, Hungertuberkulose. Historische, klinische, pathophysiologische und pathologisch-anatomische Studien und Beobachtungen an ehemaligen Insassen aus Konzentrationslagern. By A. Hottinger, O. Gsell, E. Uehlinger, C. Salzmann and A. Labhart. With a preface by Oberst K. Kistler, Zürich, director of the Militärsanitätsanstalt 4. 8°, cloth, 297 pp., with 171 Abbildungen. Basel: Benno Schwabe and Co., 1948. Ganzleinen Fr. 28.

This monograph is based on a study of 5000 severely wounded and sick soldiers hospitalized in Switzerland during 1944 and 1945. "Hungerkrankheit" may be freely translated as chronic illness due to insufficient food over a long period. The text is divided into five parts. The first constitutes a short, historical sketch, the second a clinical study of the cases of Hungerkrankheit and their treatment, the third and fourth the clinical aspects, pathogenesis and pathological anatomy of Hungerkrankheit and Hungerödem, and the fifth tuberculosis as a complication of hunger disease. The monograph is well published, but the lack of an index detracts from its value as a reference book. It should be in all the large medical libraries and in all collections on metabolism and tuberculosis.

Klinik und Therapie der Leptomeningitiden für Ärzte und Studierende. By Hermann Czickeli. 8°, paper, 95 pp. Vienna: Wilhelm Maudrich, 1948. \$2.00.

This monograph discusses the various types of meningitis. An appendix concerns the technic of lumbar puncture. Thirty-seven pages are devoted to epidemic cerebrospinal meningitis. There is a valuable table on the changes in the spinal fluid in various diseases of the central nervous system. The material is well organized. A short bibliography ends the volume. Unfortunately, there is not an index. The monograph should be available to all physicians interested in the subject.

The Rh Blood Groups and Their Clinical Effects. By P. L. Mollison, A. E. Mourant, and R. R. Race. 8°, paper, 74 pp. London: His Majesty's Stationery Office, 1948. 1s. 6d. net. Privy Council Medical Research Council Memorandum No. 19.

In this small pamphlet Dr. Mollison presents the latest information on the Rh blood groups. The text is divided into three parts: the Rh groups, clinical considerations, and Rh testing. Selected references are appended to each part.

Die vegetativen Anfälle des Herzens. By Kurt Polzer and Walter Schober. 8°, paper, 97 pp. Vienna: Wilhelm Maudrich, 1948. \$2.50.

In this monograph the heart conditions due to the action of the sympathetic nervous system are discussed. The material is well organized, proceeding from anatomy and physiology to treatment. There is a bibliography and an index. The pamphlet should be available to physicians interested in cardiology.

Erinnerungen, Erfahrungen und Methoden eines Praktikers. By Eduard von Hueber. 8°, paper, 72 pp. Vienna: Wilhelm Maudrich, 1948. \$1.00.

This small pamphlet is devoted to the achievements, ideas and methods of a general practitioner. Two thirds of the text deals with therapeutics, and the remainder with diagnosis.

Psychiatry in General Practice. By Melvin W. Thorner, M.D., D.Sc., assistant professor of neurology, The Graduate School

of Medicine, University of Pennsylvania. 8°, cloth, Philadelphia: W. B. Saunders Company, 1948. \$1.00.

This new book on psychiatry has been written primarily for the general practitioner and the internist. The language is purposely simple and nontechnical, and the material is well organized. The text is divided into two main parts. The first discusses the various types of psychiatric problems. The second deals with examination, diagnosis and treatment. Two appendixes contain important material on the classification of mental disorders and on commitment procedures including an analysis of the law in the various States. References to the literature are appended to each chapter. A good index concludes the book. The publishing is excellent in every way. The volume should be in all medical libraries and should be available to all physicians.

The Surgery of Abdominal Hernia. By George B. Mair, M.D., F.R.F.P.S.G., F.R.C.S.E., surgeon, Law Junction Hospital, Lanarkshire. 8°, cloth, 408 pp., with 138 illustrations. Baltimore: Williams and Wilkins Company, 1948. \$7.00.

Dr. Mair, in this monograph, endeavors to clarify many points of etiology and treatment. He has been concerned with the high rate of recurrence and attributes it in part to faulty technique. The work is primarily intended for those who are especially interested in hernia, including anatomists, physiologists and sociologists. The text is well written, and lists of selected references are appended to the various chapters. There is a good index. The book is well published in every way. The illustrations are excellent. The monograph should be in all medical libraries and available to all surgeons.

Human Biochemistry. By Israel S. Kleiner, Ph.D., professor of biochemistry and director of the department of physiology and biochemistry, New York Medical College, Flower and Fifth Avenue Hospitals. Second edition. 8°, cloth, 649 pp., with 77 illustrations and 5 color plates. St. Louis: C. V. Mosby Company, 1948. \$7.00.

This textbook for students, first published in 1945, has been revised, and the material brought up to date. A new chapter has been added on chemical structure in relation to biologic phenomena. Lists of references are appended to the various chapters. There is a comprehensive index. The material is well organized. The publishing is excellent. The volume should prove useful to students and others interested in the subject.

Diseases of the Adrenals. By Louis J. Soffer, M.D., associate attending physician, The Mount Sinai Hospital, New York City, and assistant clinical professor of medicine, Columbia University College of Physicians and Surgeons, New York City. Second edition. 8°, cloth, 320 pp., with 45 illustrations and 3 color plates. Philadelphia: Lea and Febiger, 1948. \$6.50.

This second edition of a standard work has been thoroughly revised and brought up to date. The material is well arranged, and the book is well published. Bibliographies are attached to the different chapters, and there is an index. The volume should be in all medical libraries.

Crime and the Mind. An outline of psychiatric criminology. By Walter Bromberg, M.D. 8°, cloth, 219 pp. Philadelphia: J. B. Lippincott Company, 1948. \$4.50.

This special monograph was developed from the clinical study of hundreds of convicted criminals. The case material was derived from the Court of General Sessions, New York, and several United States Navy prisons. The text is divided into two parts. The first discusses the legal and social environment of the criminal. The second deals with the individual criminal, including the psychopathic personality, the neurotic offender and emotional immaturity and crime. The last chapter, entitled "Cure of Crime," stresses the value of psychotherapy. There is an extensive bibliography and a good index. The text is well printed with a good type on good paper. The book should be available to all psychiatrists and psychologists.

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TO

The New England Journal of Medicine

Volume 240, January 6, 1949 to June 30, 1949

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Allen, Frank N
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Brown, Ethan A
Brues, Austin M
Buck, Robert W
Castleman, Benjamin
Chute, Richard
Cogan, David C
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KEY TO ABBREVIATIONS

bmj — Boston Medical Library
c — correspondence
cr — case report
e — editorial
mdph — Massachusetts Department of Public Health

me — notes from medical examiner
mms — Massachusetts Medical Society
mp — medical progress
misc — miscellany
nepa — New England Postgraduate Assembly

ness — New England Surgical Society
n — notice
o — obituary
* — original article

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